CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Multicenter, Open-Label Study of Tislelizumab (BGB-A317) in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma
Protocol Identifier:	BGB-A317-210 (TIRHOL: Tislelizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma)
Phase:	2
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Classical Hodgkin Lymphoma
Sponsor for France and Belgium:	LYSARC (The Lymphoma Academic Research Organisation) Centre Hospitalier Lyon Sud Bâtiment 2D 69495 Pierre-Bénite Cedex - France
Sponsor for Sites in all other Participating Countries:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, Third Floor San Mateo, California 94404, USA
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Protocol Amendment 5.0:	27 September 2022
Protocol Amendment 6.0:	23 August 2023

Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Multicenter, Open-Label Study of Tislelizumab (BGB-A317) in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

BeiGene, Ltd., Approval:

Approved Date 8/23/2023

See electronic signature	*See electronic signature*
Sponsor Medical Monitor	Date

[redacted]

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Multicenter, Open-Label Study of Tislelizumab (BGB-A317) in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

Protocol Identifier: BGB-A317-210 (TIRHOL: Tislelizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma)

This protocol is a confidential communication of BeiGene, Ltd., its subsidiaries, and LYSARC. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., one of its subsidiaries, or LYSARC.

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 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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AMENDMENT SUMMARY

This BGB-A317-210 Protocol Amendment 6.0 (23 August 2023) replaces BGB-A317-210 Protocol Amendment 5.0 (27 September 2022).

The primary purpose of Amendment 6.0 is to extend the end of the study. The main changes made in this amendment are described in the table below. Minor, editorial, and formatting changes have also been made but are not included in this summary.

Section Number	Summary of Change	Rationale for Change	Potential Impact on Safety of Patients or Study Conduct
Sponsor signature page	Electronic signature adopted	To align with health authority guidance on electronic signature use	None
Synopsis, Section 3.1, and Section 7.14	Extended the end of the study to up to approximately 2 years after enrollment of the last patient	To follow outcomes for patients who remain on the study treatment	Change to conduct of study
Synopsis, Section 3.1, and Section 7.14	Included post-trial supply program	To provide additional option for patients to receive tislelizumab at the end of the study	None

Approved Date 8/23/2023

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd. and LYSARC
Investigational Product: Tislelizumab (BGB-A317)
Title of Study: A Phase 2, Multicenter, Open-Label Study of Tislelizumab (BGB-A317) in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma
Protocol Identifier: BGB-A317-210 (TIRHOL: Tislelizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma)
Phase of Development: 2
Number of Patients: Approximately 42 patients
Study Centers: Approximately 20 to 25 centers internationally. LYSARC is the sponsor for sites in France and Belgium, and BeiGene is the sponsor for sites in all other participating countries.
Study Objectives: **Primary:** • To evaluate the efficacy of tislelizumab in patients with relapsed/refractory classical Hodgkin lymphoma (cHL), as measured by overall response rate per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator **Secondary:** • To evaluate the efficacy of tislelizumab as measured per the Lugano Classification and determined by the investigator for the following: – Complete response rate – Duration of response – Time to response • To evaluate the safety and tolerability of tislelizumab **Exploratory:** • To evaluate the efficacy of tislelizumab for the following: – Progression-free survival (PFS), as measured per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator – Overall survival – Patient-reported outcomes • To evaluate clinical outcomes per the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson et al 2016) (Appendix 5), as determined by the investigator, and ancillary exploratory studies by centralized imaging for a subset of patients (to be determined at the time of the primary analysis) • To explore tumor biomarkers of tislelizumab response, resistance, and patient prognosis (eg, programmed death ligand-1 [PD-L1], cluster of differentiation 64 [CD64], major histocompatibility complex II [MHC II], and other proteins related to disease or treatment

mechanism, presence of immune cells in the tumor microenvironment, PD-L1/programmed death ligand-2 [PD-L2] gene alteration, Epstein-Barr virus [EBV] infection status, etc). Gene mutation profiling and/or immune-related gene-expression profiling and tumor-infiltrating immune cells that are related to response or clinical benefit of tislelizumab may also be evaluated.

- To characterize the pharmacokinetics of tislelizumab
- To determine host immunogenicity to tislelizumab

Study Design:

This is a Phase 2, multicenter, open-label study of tislelizumab in patients with relapsed/refractory cHL. The primary efficacy endpoint is overall response rate (ORR), defined as the proportion of patients who achieve a best response of complete response (CR) or partial response (PR), as determined by the investigator per the Lugano Classification.

Approximately 42 patients with relapsed/refractory cHL will be enrolled into one of two cohorts based on prior therapies received: Cohort 1 will include patients who have failed to achieve a response or who have had disease progression after autologous hematopoietic stem cell transplantation (HSCT); Cohort 2 will include patients who have failed to achieve a response or who have had disease progression after at least 1 prior systemic regimen for cHL and are not candidates for autologous or allogeneic HSCT. The primary efficacy analysis will be performed for both cohorts combined, and subgroup analyses by cohorts will be performed.

All patients will receive tislelizumab 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or study withdrawal for other reasons. The end of the study is expected to occur up to approximately 2 years after enrollment of the last patient. Patients who remain on study treatment at the end of the study may have an opportunity to receive tislelizumab in a separate rollover or extension study or post-trial supply program. A patient in Cohort 2 who achieves a complete remission and is otherwise a candidate for autologous HSCT may proceed to autologous HSCT at the discretion of the investigator and with approval from the sponsor. The investigator should contact the sponsor to discuss autologous HSCT and tislelizumab maintenance therapy post-autologous HSCT.

Treatment with tislelizumab will be open label. Screening procedures must be performed within 28 days prior to the first dose of study treatment, unless noted otherwise. Once all screening assessments have been completed and study eligibility has been confirmed, study treatment must commence within 14 days of confirmation, which is within the 28-day screening window prior to the first dose of study treatment.

Study Assessments:

At screening, written informed consent, eligibility based on inclusion and exclusion criteria, and medical history will be collected. Baseline assessments will include pulmonary function test, hepatitis B and C serologies (and DNA levels, if necessary), and echocardiogram or multigated acquisition scan. HIV results will be recorded if previously known. Throughout the study, vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, complete blood count with differential, and serum chemistry panel will be monitored. Additional assessments will include height and weight, 12-lead electrocardiogram (ECG), erythrocyte sedimentation rate, pregnancy test (if applicable), and thyroid function evaluation.

Tumor assessments will be performed using positron emission tomography-computed tomography (PET-CT) at screening, at Week 12 starting from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks thereafter until disease progression. Computed tomography (CT) with contrast will be performed at screening and every 24 weeks starting from Cycle 1 Day 1 until disease progression. Total body magnetic resonance imaging (MRI) or CT without contrast of the chest plus MRI of the

neck, abdomen, and pelvis is allowed if CT with contrast is contraindicated. At time points in which a CT scan with contrast is required, PET-CT may be adequate if the CT portion of the PET-CT is of diagnostic quality and contrast is administered.

Patient-reported outcomes (European Quality of Life 5-Dimensions 5-Levels health questionnaire [EQ-5D-5L] and European Organisation for Research and Treatment of Cancer Quality of Life cancer core questionnaire [EORTC QLQ-C30]) will also be assessed.

Pharmacokinetics (PK) and immunogenicity analyses will be conducted. For biomarker analyses, archival and/or fresh tumor tissue samples will be collected.

Safety assessments will include a review of adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, pulmonary and cardiac function tests, electrocardiograms, ECOG performance status, and vital signs. All AEs and laboratory safety measurements will be graded per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

A Safety Follow-up Visit will be mandatory. All AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after last dose of study treatment. A Safety Monitoring Committee will review safety data after at least 20 patients have been on treatment for at least 9 weeks.

Key Eligibility Summary and Patient Selection:

Adult patients (≥ 18 years of age at time of informed consent) with a histologically confirmed diagnosis of cHL based on the World Health Organization (WHO) 2017 classification of tumors of hematopoietic and lymphoid tissue, and the presence of measurable disease, will be eligible for this study. Archival tissue (block or approximately 15 unstained slides) or fresh tissue are acceptable to be sent together with a pathology report to the central laboratory for retrospective pathology confirmation of cHL diagnosis and biomarker analysis.

Patients must have relapsed cHL (disease progression after PR or CR to the most recent therapy) or refractory cHL (failure to achieve PR or CR to most recent therapy). Patients will be allocated to 1 of 2 cohorts based on the following criteria:

- Cohort 1: Patients who have failed to achieve a response or who have had disease progression after autologous HSCT
- Cohort 2: Patients who have received at least 1 prior systemic regimen for cHL and are not candidates for autologous or allogeneic HSCT

Patients meeting either criteria defined above will be enrolled within Cohort 1 or 2. Patients will have adequate performance status and organ function and will not have active autoimmune disease and active infection with hepatitis B or C, HIV, or known history of human T-cell lymphotropic virus.

Investigational Product, Dose, and Mode of Administration:

Tislelizumab (200 mg) will be administered intravenously. A cycle is 3 weeks (21 days) in duration.

Statistical Methods:

Analysis Sets:

The Safety Analysis Set includes all patients who receive at least 1 dose of tislelizumab.

This will be the primary analysis set for the efficacy and safety analyses. Efficacy and safety analyses will be performed for both cohorts combined.

The PK Analysis Set includes all patients for whom valid tislelizumab PK parameters can be estimated.

Primary Efficacy Endpoint Analysis:

The primary endpoint is ORR assessed by the investigator per the Lugano Classification (Cheson et al 2014) (Appendix 4). The ORR is defined as the proportion of patients achieving a best response of CR or PR.

Best overall response is defined as the best response recorded from the first dose of tislelizumab until data cut or the start of a new anti-lymphoma therapy. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders. ORR and its corresponding Clopper-Pearson 95% confidence interval (CI) will be presented. The proportion for each of the response categories will also be summarized.

The primary efficacy analysis for both cohorts combined will be conducted at least 12 weeks after the last patient has been dosed, either having undergone the first response assessment or having withdrawn prior to the first response assessment. A separate end-of-study analysis will be performed, details of which will be provided in the Statistical Analysis Plan (SAP).

The historical control ORR is assumed to be approximately 45% based on previous clinical trials (Moskowitz et al 2013). The null and alternative hypotheses are set as follows:

H_0: ORR = 0.45 for Cohort 1 and Cohort 2 combined

H_a: ORR > 0.45 for Cohort 1 and Cohort 2 combined

A binomial exact test will be performed to test the hypothesis. If the 1-sided p-value is less than or equal to 0.05 (which is equivalent to observing 25 or more responders out of 42 patients), it will be concluded that single agent tislelizumab statistically significantly increases ORR compared to the historical control. The superiority of single agent tislelizumab will be demonstrated at 1-sided level alpha of 0.05. A 2-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the rate estimate; a 2-sided 90% CI will also be constructed to be consistent with the 1-sided 95% confidence bound.

Secondary Efficacy Endpoint Analyses:

The CR as determined by the investigator will be summarized and the corresponding Clopper-Pearson 95% CIs will be calculated. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders.

Duration of response will be analyzed using the Kaplan-Meier method. Time to response will be analyzed using descriptive statistics such as mean, median, and standard deviation. Only patients who have achieved an overall response will be included in the analysis of duration of response and time to response.

Exploratory Efficacy Analyses:

The distribution of PFS will be estimated using the Kaplan-Meier method. PFS at selected time points will be estimated with its 95% CI using Greenwood's formula. Details of the censoring rules for PFS will be provided in the SAP.

Overall survival will be censored at the last known date alive. Overall survival will be analyzed similarly as for PFS.

The EORTC QLQ-C30 and EQ-5D-5L and questionnaires will be summarized for each assessment time point. The proportion of patients with significant changes from baseline in the questionnaires may be summarized as applicable.

Clinical outcomes by tumor assessment will be summarized using the LYRIC criteria (Cheson et al 2016) (Appendix 5).

Efficacy variables (eg, ORR and PFS) will be correlated to biomarker expression levels to identify a potential biomarker defining a subset that is more sensitive to the programmed cell death-1 (PD-1) treatment.

Correlation between steady-state trough serum concentration of tislelizumab and efficacy or safety endpoints may be explored.

Safety Analyses:

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry), vital signs, and physical examination will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

Safety data will be monitored throughout the study. At approximately 9 weeks after the 20th patient has been dosed, data from the first 20 patients in the combined cohorts will be compared against pre-specified safety stopping criteria. The stopping criteria will be applied for deaths from causes other than disease progression (non-PD), treatment-emergent SAEs, and treatment-emergent Grade 3 or higher immune-related AEs and are based on cutoffs representing a greater than 85% Bayesian posterior probability of exceeding a set event rate threshold where each event rate threshold is based approximately in reference to the results of approved anti-PD-1 treatments, including nivolumab (Armand et al 2018, Opdivo® US Prescribing Information). As enrollment is being discontinued, safety data will be analyzed next at the time of primary efficacy analysis.

Sample Size Considerations:

A total of approximately 42 patients will be enrolled.

Assuming an alternative ORR of 65% compared to the null ORR of 45% in Cohort 1 and Cohort 2 combined, using a binomial exact test, the power to reject the null hypothesis with 42 patients at a 1-sided alpha of 0.05 is greater than 80%.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
cHL	classical Hodgkin lymphoma
CD	cluster of differentiation, such as CD4, CD8, etc.
CR	complete response
CT	computed tomography
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D-5L	European Quality of Life 5-Demention 5-Level
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
GHS/QoL	Global Health Status/Quality of Life
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDT	high-dose chemotherapy
HL	Hodgkin lymphoma
HSCT	hematopoietic stem cell transplantation
ICH	International Council for Harmonisation
IFN	interferon

Abbreviation	Definition
IgG	Immunoglobulin G
IL	interleukin
irAE	immune-related adverse event
LYRIC	Lymphoma Response to Immunomodulatory Therapy Criteria
LYSA	The Lymphoma Study Association
LYSARC	The Lymphoma Academic Research Organisation
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	overall response rate
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death ligand-1, programmed death receptor ligand-1, programmed death-1 ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
QLQ-C30	European Organisation of Research and Treatment and Quality of Life Core 30
SAE	serious adverse event
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
tislelizumab	BGB-A317
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a B-cell lymphoid malignancy with an increased incidence in young adults between 15 and 30 years of age as well as in patients 55 years and older. The World Health Organization (WHO) classifies HL into 2 main types: classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL). Classical HL accounts for 95% and NLPHL accounts for 5% of all HL (Weber et al 2015).

The hallmark of cHL is the presence of malignant, multinucleated Reed-Sternberg (RS) cells. These cells are of follicular center B-cell origin and constitute < 1% of cells in the affected lymph nodes, within a characteristic reactive cellular background of normal lymphocytes, eosinophils, and histiocytes (McDermott and Atkins 2013). Despite their B-cell origin, RS cells have a global loss of B-cell gene expression. They do not produce immunoglobulin or have functional B-cell antigen receptors (Marafioti et al 2000). Various cytokines, chemokines, growth factors and their receptors (including but not limited to interleukins [IL1 to IL10], interferon [IFN], tumor necrosis factor-alpha [TNF-α], transforming growth factor-beta [TGF-β], granulocyte-colony stimulating factor [G-CSF], and granulocyte-monocyte colony stimulating factor [GM-CSF]), play a role in creating this microenvironment (Desai et al 2016; Riley 2009). The T-cell infiltrate in cHL is composed predominantly of Th2 and regulatory T cells and generally lacks Th1 cells, cluster of differentiation 8 (CD8) cytotoxic T cells, and natural killer cells, resulting in an inhibition of cytotoxic anti-tumor immune responses (Ohshima et al 2003; Opdivo® US Prescribing Information).

Factors in determining the initial choice of therapy for HL include the histology of the disease (cHL or NLPHL), the anatomical stage of disease (limited or advanced disease), the presence of poor prognostic features, the presence of constitutional symptoms, and the presence of bulky disease. In general, patients with early-stage disease are treated with combined modality strategies using an abbreviated course of chemotherapy followed by involved-field radiation, while those with advanced-stage disease receive a longer course of chemotherapy.

Despite a high cure rate with initial therapy, approximately 5% to 10% of HL patients will have primary refractory disease, and 10% to 30% of patients will relapse after achieving an initial complete response (CR) (Ansell 2012). Treatment for relapsed/refractory disease includes high-dose chemotherapy (HDT) with autologous stem cell transplantation (auto-SCT), which has been associated with 5-year overall survival rates of 79%, 59%, and 17% for patients in complete remission, partial remission, or those with resistant disease at the time of HDT/auto-SCT, respectively (Stathis and Younes 2015). Brentuximab vedotin is a CD30-directed antibody-monomethyl auristatin E conjugate, which is associated with a CR rate of 34% and an overall response rate (ORR) of 75% (Younes et al 2012a). In 2011, brentuximab vedotin was approved by the US Food and Drug Administration (FDA), and later in Europe, for the treatment of patients with relapsed HL after failure of auto-SCT or patients who are not transplant candidates and failed at least 2 prior chemotherapy regimens (Adcetris® US Prescribing Information). Two monoclonal antibodies directed against programmed cell death-1 (PD-1), nivolumab and pembrolizumab, also have been approved by the US FDA. Nivolumab is a fully human immunoglobin G4 (IgG4) monoclonal antibody for the treatment of patients with cHL who had

relapse or disease progression after HDT/auto-SCT and post-transplantation brentuximab vedotin. Pembrolizumab is a humanized IgG4 kappa monoclonal antibody for the treatment of patients with relapsed or refractory cHL (Chen et al 2017). Other therapies that have been examined for the treatment of relapsed/refractory HL include panobinostat, a histone deacetylase inhibitor (Younes et al 2012b); everolimus, a rapamycin inhibitor (Johnston et al 2010); and lenalidomide, an immunomodulatory agent (Fehniger et al 2011).

1.2. Immune Checkpoint Inhibitors

The immune checkpoint-inhibitory receptor PD-1 is mainly expressed in activated T-cells, including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (Ohshima et al 2002). It is believed that PD-1 plays an important role in the immune modulation of tumor progression by regulating the key inhibitory signaling in T cells that are engaged by their ligands. The PD-1 signaling cascade negatively regulates the T-cell receptor, thereby attenuating T-cell proliferation and functional activities and leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of the programmed death ligand-1 (PD-L1) is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as IFN-γ (gamma) and IFN-α (alpha) in the tumor microenvironment (Sirohi et al 2008).

1.2.1. Pembrolizumab

Pembrolizumab, a humanized anti-PD-1 IgG4 kappa monoclonal antibody, has been approved by the US FDA for the treatment of patients with unresectable or metastatic melanoma; metastatic non-small cell lung carcinoma in which tumors express PD-L1 and have progressed on or after platinum-containing chemotherapy; recurrent or metastatic head and neck squamous cell carcinoma that has progressed on or after platinum-containing chemotherapy; and relapsed/refractory cHL (Keytruda® US Prescribing Information).

In a study of 31 patients with cHL who received pembrolizumab after failing brentuximab vedotin (71% of whom had undergone prior auto-SCT), the ORR was 65%, with a CR rate of 16% and a partial response (PR) rate of 48%. The majority of responses (70%) lasted > 24 weeks, with a median follow-up of 17 months. Progression-free survival (PFS) was 69% at 24 weeks and 46% at 52 weeks. For a subset of patients who had undergone auto-SCT (n=22), the ORR was 73%, with a CR rate of 14% and a PR rate of 59% (Armand et al 2016).

In a study of 210 patients with relapsed/refractory cHL, 3 cohorts were analyzed: (1) patients who had disease progression after auto-SCT and subsequent brentuximab vedotin; (2) patients who were ineligible for auto-SCT due to prior salvage chemotherapy and brentuximab vedotin; and (3) patients who had disease progression after auto-SCT but did not receive subsequent brentuximab vedotin. After treatment with pembrolizumab, the ORR across all cohorts was 69.0%, with a CR rate of 22.4%, PR rate of 46.7%, and stable disease (SD) rate of 14.8%. In patients who were ineligible for auto-SCT due to prior salvage chemotherapy and brentuximab vedotin, the ORR was 64.2%. Overall survival was 99.5% at 6 months and 97.5% at 9 months. PFS was 72.4% at 6 months and 63.4% at 9 months (Chen et al 2017). No difference in ORR or CR rate was observed based on which prior therapies patients had received.

In a study of 304 patients with relapsed/refractory cHL, patients who had received at least 1 prior multi-agent chemotherapy regimen were randomized 1:1 to receive either pembrolizumab or brentuximab vedotin. The median PFS was 13.2 months (95% CI, 10.9-19.4) for patients treated with pembrolizumab versus 8.3 months (95% CI, 5.7-8.8) for patients treated with brentuximab vedotin. Pembrolizumab was found to reduce the risk of disease progression or death by 35% (HR=0.65 [95% CI, 0.48-0.88; p=0.0027]). The ORR was 66% (95% CI, 57-73), with a CR rate of 25%, for those treated with pembrolizumab versus ORR 54% (95% CI, 46-62) and CR rate 24% for those treated with brentuximab vedotin. The median duration of response (DOR) was 20.7 months with pembrolizumab and 13.8 months with brentuximab vedotin (Kuruvilla et al 2021).

1.2.2. Nivolumab

Nivolumab, a fully human anti-PD-1 IgG4 monoclonal antibody, has been approved by the US FDA for the treatment of patients with proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog V600 wild-type and mutation-positive unresectable or metastatic melanoma as a single agent and in combination with ipilimumab for unresectable metastatic melanoma; metastatic non-small cell lung cancer that has progressed on or after platinum-based chemotherapy; advanced renal cell carcinoma after prior anti-angiogenic therapy; and cHL that has relapsed or progressed after HDT/auto-SCT and post-transplantation brentuximab vedotin.

In 2 studies of nivolumab monotherapy in patients with cHL whose disease had relapsed or progressed after auto-SCT, a total of 258 patients were evaluated, of which 195 patients had received prior treatment with brentuximab vedotin. The ORR was 69% (179 patients), with a CR rate of 14% (37 patients) and a PR rate of 55% (142 patients). The median time to response was 2.0 months. (Opdivo® US Prescribing Information).

1.2.3. Checkpoint Inhibitors and Immune-Related Adverse Events

Immune checkpoint inhibitors have been associated with immune-related toxicities that may develop during immunotherapy treatment. As such, clinical practice guidelines that address the management of immune-related adverse events (irAEs) in patients treated with immune checkpoint inhibitor therapies have recently been published (Brahmer et al 2018).

The most commonly reported irAEs have been cutaneous, gastrointestinal, and musculoskeletal. The incidence of cutaneous irAEs such as rash/inflammatory dermatitis, bulbous dermatoses, and severe cutaneous adverse reactions have ranged from 17% to 37%, while gastrointestinal toxicities such as diarrhea have been reported in up to 54% and colitis in 8% to 27% of patients. Hepatotoxicity has been seen in 2% to 10% of patients treated with nivolumab and pembrolizumab monotherapy. Musculoskeletal irAEs such as arthritis, polymyalgia-like syndromes, and myositis have been reported in up to 40% of patients (Brahmer et al 2018).

Lung, endocrine, and hematologic toxicities are less common, with incidences ranging from 2% to 11%. In a meta-analysis of 20 studies of patients treated with anti-PD-1 therapies, the overall incidence of pneumonitis was 2.7% (Nishino et al 2016). Endocrine toxicities, including primary hypothyroidism, hyperthyroidism, primary adrenal insufficiency, hypophysitis, and diabetes, have been seen in approximately 10% of patients treated with immune checkpoint inhibitors, as reported in a meta-analysis of 7,551 patients from 38 randomized trials (Barroso-Sousa et al 2018). Hematologic toxicities include autoimmune hemolytic anemia, acquired thrombotic

thrombocytopenic purpura, hemolytic uremic syndrome, aplastic anemia, lymphopenia, immune thrombocytopenia, and acquired hemophilia. Of these, anemia and thrombocytopenia were most frequently reported: anemia 11% (5.4% Grades 3 and 4) and thrombocytopenia 8% (4.3% Grades 3 and 4).

Rare toxicities, reported in 2% or fewer patients, include renal, neurologic, cardiovascular, and ocular toxicities. Renal toxicities are uncommon in patients treated with immune checkpoint inhibitors, with acute kidney insufficiency reported in 1% to 2% of patients treated with nivolumab and pembrolizumab. Neurologic toxicities reported in patients treated with immune checkpoint inhibitors include myasthenia gravis, Guillain-Barre Syndrome, peripheral neuropathy, autonomic neuropathy, aseptic meningitis, encephalitis, and transverse myelitis. Cardiovascular toxicities have been rare in patients treated with immune checkpoint inhibitors, reported in < 0.1% of patients, but they can be potentially life-threatening. Cardiovascular complications reported in these patients include myocarditis, myocardial fibrosis, cardiomyopathy, heart failure, conduction abnormalities, cardiac arrest, pericarditis, and pericardial effusions. While ocular toxicities such as uveitis/iritis, episcleritis, and blepharitis have been reported, they are uncommon (Brahmer et al 2018).

1.3. Tislelizumab

Tislelizumab (also known as BGB-A317) is a humanized IgG4 variant monoclonal antibody directed against PD-1. It is being developed for the treatment of human malignancies. Tislelizumab was manufactured under Good Manufacturing Practice quality control systems. The clinical trial drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolality. The suggested administration route is intravenous infusion after the appropriate dilution in 0.9% sodium chloride solution.

1.3.1. Nonclinical Data of Tislelizumab

For details of the nonclinical data for tislelizumab to date, see the current Tislelizumab Investigator's Brochure.

Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity (K_D = 0.15 nM), as demonstrated by receptor binding assays based on surface plasmon resonance. Tislelizumab competitively blocks the binding of both PD-L1 and programmed death ligand-2 (PD-L2), inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, the humanized antibody consistently and dose-dependently enhanced the functional activity of human T cells and pre-activated primary peripheral blood mononuclear cells. In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models.

The IgG4 variant antibody has very low binding affinity to effector receptors, including gamma Fc receptors (FcγRs) and C1q, by in vitro assays and has low or no antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effect in humans. Unlike natural IgG4 antibody, tislelizumab has no observable Fab-Arm exchange activity by the in vitro assay, suggesting that the antibody would be stable in vivo and unlikely to form a bispecific antibody.

Tislelizumab binds to the cynomolgus monkey and human PD-1 with similar affinity but does not bind to mouse PD-1 due to the significant sequence divergence from human and monkey PD-1.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues and no effect on cytokine release was observed in a human whole blood assay. The toxicokinetic profile was well characterized, with dose-proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on systemic exposure.

1.3.2. Clinical Pharmacology

An interim pharmacokinetics (PK) analysis (cutoff date 28 August 2017) was conducted by noncompartmental methods using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, or 10 mg/kg once every 2 weeks, or 2.0 mg/kg, 5.0 mg/kg, or 200 mg once every 3 weeks (Phase 1a, Parts 1, 2, and 3, and Phase 1b in Study BGB-A317_Study_001) and patients who received doses of 200 mg once every 3 weeks (Phase 1 of Study BGB-A317-102). The maximum observed serum concentration (C_{max}) and area under the serum concentration-time curve (AUC) increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration at steady state. Preliminary PK data from 28 patients who were administered 200 mg once every 3 weeks (Phase 1a, Part 3 and Study BGB-A317-102) showed that tislelizumab concentrations after the first 200-mg dose were between the range of concentrations observed after 2-mg/kg and 5-mg/kg doses.

A population PK analysis showed that a 3-compartment model with first-order elimination best described the PK data. Systemic clearance of tislelizumab was 0.164 L/day; volume of distribution at steady state (V_{ss}) was 5.238 L; and terminal half-life ($t_{1/2}$) was approximately 25.5 days. Race, gender, and body weight were not significant covariates on the systemic clearance of tislelizumab, which supports fixed dosing across different ethnic groups.

In a noncompartmental analysis for Study BGB-A317_Study_001 and Study BGB-A317-102, a comparison of intensive PK data after a single intravenous (IV) infusion of tislelizumab indicated that dose-normalized exposure ($AUC_{0\text{-}14day}$) was consistent between non-Chinese patients (n = 91, mostly Caucasian) and Chinese patients (n = 20). This shows that the PK of tislelizumab is comparable between Chinese and non-Chinese patients. Additionally, $AUC_{0\text{-}14day}$ was also consistent across Asian (n = 27, including 20 Chinese and 7 non-Chinese Asian) and Caucasian (n = 80) patients. This finding is consistent with the evidence that ethnic differences in PK are not expected for therapeutic monoclonal antibodies (Chiba et al 2014, Matsushima et al 2015, Zhou et al 2012).

Similarly, a comparison of trough (predose) and peak (end-of-infusion) concentration data after multiple IV infusions of tislelizumab 200 mg administered once every 3 weeks showed that the levels were generally similar for Chinese and non-Chinese patients and for different tumor types (advanced solid tumors and cHL).

1.3.3. Prior Clinical Experience With Tislelizumab

As of 01 September 2018, there were 18 ongoing studies with tislelizumab, including 7 with available preliminary data. Of the ongoing monotherapy studies, clinical data from BGB A317_Study_001, BGB-A317-102, and BGB A317-203 are summarized below.

For details of the current, ongoing studies with tislelizumab, see the current Tislelizumab Investigator's Brochure.

1.3.3.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 is a 2-stage study: Phase 1a (dose escalation and dose-finding) and Phase 1b (efficacy and safety in select tumor types). A total of 451 patients were enrolled. As of 27 April 2018, 148 (32.8%) patients remained on study; 49 (10.9%) were still receiving tislelizumab treatment; and 99 (22.0%) were in follow-up.

The maximum administered dose was 10 mg/kg administered once every 2 weeks. The maximum tolerated dose was not identified. Only 1 dose-limiting toxicity of Grade 3 colitis occurred at the 5 mg/kg dose administered once every 2 weeks. Based on the results of 103 patients in the dose-escalation and dose-expansion part of the Phase 1a study, a dose of 5 mg/kg administered once every 3 weeks was selected for use in exploring tislelizumab activity in multiple tumor types in the Phase 1b study. An additional cohort (Phase 1a, Part 3) was added to evaluate fixed dosing at 200 mg once every 3 weeks.

As of 27 April 2018, of the 451 patients enrolled, 255 patients (56.5%) experienced ≥ 1 treatment-emergent adverse event (TEAE) assessed by the investigator as related to tislelizumab. The most commonly occurring TEAEs found to be related to tislelizumab were Fatigue (12.9%), Rash (8.4%), Nausea (7.1%), and Diarrhoea (6.9%). A total of 125 patients (27.7%) experienced ≥ 1 immune-related TEAE; of these, 22 patients (4.9%) had events found to be severe (≥ Grade 3). There were 33 patients (7.3%) who experienced a TEAE that led to treatment discontinuation. Of these, 23 patients (5.1%) experienced events that were assessed as related to tislelizumab. A total of 11 patient deaths were reported; 2 (0.4%) were considered related to study drug by the investigator.

As of 27 April 2018, 116 patients and 321 patients were efficacy-evaluable in the Phase 1a and Phase 1b studies, respectively. In the Phase 1a study, 21 patients achieved a CR or PR, for an ORR of 18.1%. In the Phase 1b study, 39 patients achieved a CR or PR, for an ORR of 12.1%.

1.3.3.2. Study BGB-A317-102

Study BGB-A317-102 is a 2-phase, nonrandomized, Phase 1/2 study of tislelizumab monotherapy in Chinese patients with advanced solid tumors. The Phase 1 portion includes 2 substudies: (1) dose verification and (2) PK evaluation of the products derived from 2 manufacturing processes and scales. The Phase 2 portion is an indication-expansion study.

A total of 294 patients were enrolled. As of 11 May 2018, 196 patients (66.7%) experienced ≥ 1 TEAE assessed by the investigator as related to tislelizumab. The most commonly occurring TEAEs found to be related to tislelizumab were Aspartate aminotransferase (AST) increased (18.0%), Alanine aminotransferase (ALT) increased (15.3%), Anaemia (12.6%), and Blood bilirubin increased (10.2%). A total of 133 patients (45.2%) experienced ≥ 1 immune-related TEAE; of these, 14 patients (4.8%) had events found to be severe (≥ Grade 3). There were 17 patients (5.8%) who experienced a TEAE that led to treatment discontinuation. Of these, 4 patients (1.4%) had events assessed as related to tislelizumab. Fourteen patients (4.8%) died as a result of TEAEs. One patient death was considered possibly related to study drug treatment.

As of 11 May 2018, there were 204 efficacy-evaluable patients. Of these, 28 patients achieved a CR or PR for an ORR of 13.7%.

1.3.3.3. Study BGB-A317-203

Study BGB-A317-203 is a single-arm multicenter Phase 2 study of tislelizumab monotherapy in Chinese patients with relapsed or refractory cHL. A total of 70 patients were enrolled. As of 25 May 2018, 67 patients (95.7%) remained on study; 53 (75.7%) were still receiving tislelizumab treatment; and 14 (20.0%) were in follow-up.

As of 25 May 2018, the ORR was 85.7%, with a CR rate of 61.4%, as assessed by independent central review. Of the 43 patients with a CR, 38 achieved a CR at the first on-study response assessment. The estimated 6-month PFS rate was 80% (Song et al 2018). Overall, 63 patients (90.0%) experienced a TEAE and 62 patients (88.6%) experienced a drug-related TEAE. Nine patients (12.9%) experienced a severe (≥ Grade 3) drug-related TEAE. Immune-related TEAEs were reported in 23 patients (32.9%). Of these, 5 patients had TEAEs of ≥ Grade 3: 2 patients had Pneumonitis and 1 patient each had Organizing pneumonia, Nephritis (Focal segmental glomerulosclerosis), and Increased creatine phosphokinase. A total of 4 patients (5.7%) discontinued treatment due to a TEAE. One patient died due to disease progression (Song et al 2018).

1.3.3.4. Immune-Related Reactions

In patients treated with tislelizumab monotherapy, a number of immune-related adverse events (irAEs) have been reported, including hepatitis; pneumonitis; colitis and diarrhea; and endocrinopathies such as diabetes mellitus, thyroid disorders, adrenal disorders, and hypophysitis. Other reported events include myocarditis, rhabdomyolysis, myositis, autoimmune encephalitis, nephritis, pancreatitis, myalgia, arthritis, skin reactions, mucositis, and autoimmune eye disorders. Fatal immune-related adverse events have occurred. For additional details of the irAEs seen to date in patients treated with tislelizumab monotherapy, see the current Tislelizumab Investigator's Brochure.

1.3.4. Rationale for Using Tislelizumab in the Treatment of cHL

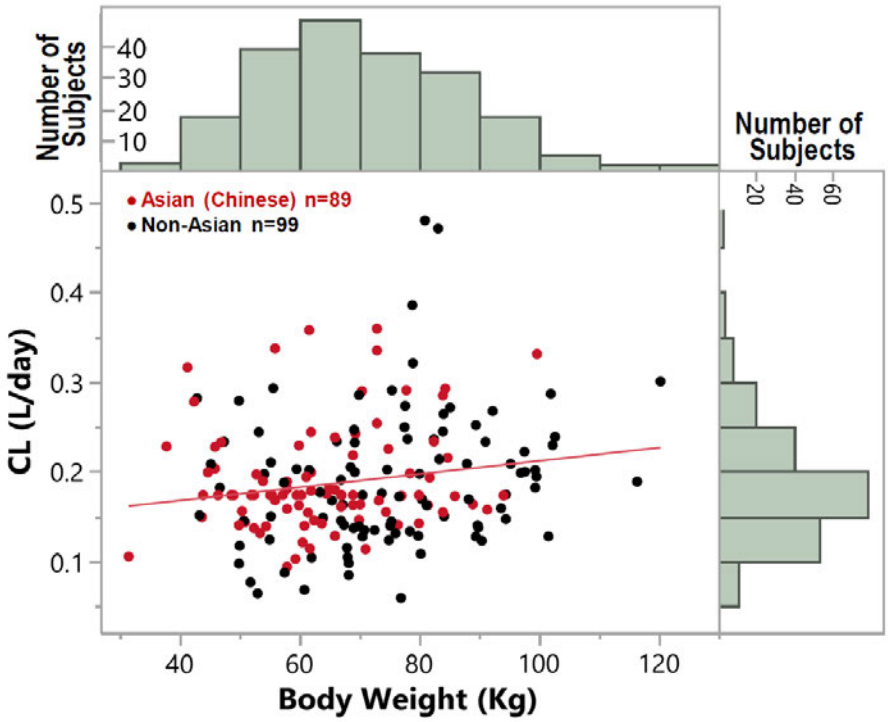
PD-L1 overexpression in HL cells may indicate a genetically determined vulnerability of lymphoma cells to PD-1 blockade (Ansell et al 2015). Furthermore, clinical data from other PD-1 inhibitors, nivolumab and pembrolizumab, in cHL, coupled with early data of tislelizumab in Chinese patients with cHL, support the rationale to further explore tislelizumab in a broader population of patients with cHL.

The rationale for this study is further supported by in vivo tumor growth inhibition studies, which demonstrated that tislelizumab has significantly higher anti-tumor activities than nivolumab or pembrolizumab in mouse models carrying allogenic human cancer cells and peripheral blood mononuclear cells (BeiGene internal data).

The efficacy of tislelizumab has also been demonstrated in 70 Chinese patients with cHL. In these patients treated with tislelizumab monotherapy, the ORR was 85.7%, with a CR rate of 61.4%. Tislelizumab was generally well tolerated. The reported ORR and CR rates are higher than those observed with other PD-1 inhibitors. Therefore, study of this molecule in a global setting is

warranted. In light of these preliminary safety and efficacy results for monotherapy tislelizumab, coupled with the finding that patients' body weight is not a significant covariate in the clearance of tislelizumab (Figure 1), a fixed dose of tislelizumab at 200 mg once every 3 weeks will be explored in this study.

Figure 1: Lack of Correlation Between Clearance and Body Weight (Study BGB-A317_Study_001, Study BGB-A317-102, and Study BGB-A317-203)



Data cutoff 28 August 2017.

1.3.5. Rationale for Selection of Tislelizumab Dose

The fixed dose of 200 mg was selected based on nonclinical studies and available clinical data, as described below.

In a Phase 1 study of tislelizumab (Study BGB-A317_Study_001), a range of doses was tested (0.5 mg/kg to 10 mg/kg once every 2 weeks [n=62] and 2 mg/kg to 5 mg/kg once every 3 weeks [n = 41]) with no maximum tolerated dose defined at the highest dose examined. Rates of treatment-related adverse events (AEs) and serious adverse events (SAEs) observed in patients who received tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose dependence across these regimens. Consequently, patients receiving a fixed dose of tislelizumab 200 mg once every 3 weeks are expected to have similar AE profiles to those treated with 2 mg/kg and 5 mg/kg once every 3 weeks.

Confirmed ORR ranged from 5% to 14% in patients treated with 2 mg/kg and 5 mg/kg once every 2 weeks, and from 17% to 37% in patients treated at the same dose levels once every 3 weeks. Therefore, clinical activity of tislelizumab is expected to be maintained in patients receiving 200 mg once every 3 weeks.

In a Phase 1a PK study conducted in Australia, serum concentrations of tislelizumab showed linear relationships for doses from 0.5 mg/kg once every 2 weeks to 10 mg/kg once every 2 weeks. Furthermore, according to the results of a population PK analysis, there was no significant correlation between patient weight and the in vivo clearance rate of tislelizumab. This conclusion supported the hypothesis of fixed-dose administration. A 200-mg fixed dose (ie, body weight adjusted dose between 3 mg/kg and 4 mg/kg) administered once every 3 weeks was expected to result in serum exposure between those associated with doses between 2 mg/kg and 5 mg/kg.

This prediction was corroborated by simulations conducted using population PK analysis and preliminary PK data from 28 patients who were administered tislelizumab 200 mg once every 3 weeks (Study BGB-A317_Study_001, Phase 1a, Part 3 and Study BGB-A317-102). In these studies, tislelizumab concentrations after the first 200-mg dose were found to be within the concentrations observed after 2 mg/kg and 5 mg/kg doses. Additionally, the PK profile of tislelizumab was consistent between Chinese patients and Caucasian patients.

No unexpected treatment-related AEs occurred in the 200-mg fixed-dose cohort (Study BGB-A317-Study-001, Phase 1a, Part 3) when compared with body-weight-based cohorts. In study BGB-A317-203, patients with cHL treated with a fixed dose of 200 mg once every 3 weeks reported high ORR and CR rates and manageable toxicity.

In summary, 200 mg administered once every 3 weeks was selected as the recommended dose for pivotal studies based on the totality of evidence available, including clinical PK, safety, and efficacy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

To evaluate the efficacy of tislelizumab in patients with relapsed/refractory classical Hodgkin lymphoma, as measured by the overall response rate per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator.

2.1.2. Secondary Objectives

- To evaluate the efficacy of tislelizumab as measured per the Lugano Classification and determined by the investigator for the following:
  - Complete response rate
  - Duration of response
  - Time to response
- To evaluate the safety and tolerability of tislelizumab

2.1.3. Exploratory Objectives

- To evaluate the efficacy of tislelizumab for the following:
  - Progression-free survival, as measured per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator
  - Overall survival
  - Patient-reported outcomes
- To evaluate clinical outcomes per the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson et al 2016) (Appendix 5), as determined by the investigator, and ancillary exploratory studies by centralized imaging for a subset of patients (to be determined at the time of the primary analysis)
- To explore tumor biomarkers of tislelizumab response, resistance, and patient prognosis (eg, PD-L1, CD64, major histocompatibility complex II [MHC II], and other proteins related to disease or treatment mechanism, presence of immune cells in the tumor microenvironment, PD-L1/PD-L2 gene alteration, Epstein-Barr virus [EBV] infection status, etc). Gene mutation profiling and/or immune-related gene-expression profiling and tumor-infiltrating immune cells that are related to response or clinical benefit of tislelizumab may also be evaluated.
- To characterize the pharmacokinetics of tislelizumab
- To determine host immunogenicity to tislelizumab

2.2. Study Endpoints

2.2.1. Primary Endpoint

The overall response rate, defined as the proportion of patients who achieve a best response of complete response or partial response by positron emission tomography-computed tomography (PET-CT) per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator.

2.2.2. Secondary Endpoints

- Efficacy endpoints assessed by the investigator using the Lugano Classification:
  - Complete response rate, defined as the proportion of patients who achieve a best response of complete response
  - Duration of response, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first
  - Time to response, defined as the time from the date of the first dose of tislelizumab to the time the response criteria are first met
- Safety and tolerability of tislelizumab, as defined by:
  - The incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0
  - Changes in vital signs, physical findings, and clinical laboratory results

2.2.3. Exploratory Endpoints

- Progression-free survival, as assessed by the investigator using the Lugano Classification and defined as the time from the first dose of tislelizumab to the date of disease progression or death, whichever occurs first
- Overall survival, defined as the time from the first dose of tislelizumab to the date of death from any cause
- Patient-reported outcomes (PRO) as measured via the European Organisation of Research and Treatment and Quality of Life Core 30 (QLQ-C30) and the European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L). The key end points include Global Health Status/Quality of Life (GHS/QoL), physical function and role function scales, and symptoms of fatigue, dyspnea, diarrhea, and pain measured by the QLQ-C30
- Clinical outcomes (eg, progression-free survival and duration of response) per the LYRIC criteria (Cheson et al 2016) (Appendix 5), as determined by the investigator, and ancillary exploratory studies by centralized imaging for a subset of patients (to be determined at the time of the primary analysis)

- Status of exploratory biomarkers in the study population and their association with disease status, response, and/or resistance mechanisms of tislelizumab
- Pharmacokinetics of tislelizumab: summary of serum concentrations of tislelizumab, including but not limited to tislelizumab trough serum concentration (C_{trough})
- Immunogenicity of tislelizumab: assessment of the incidence of antidrug antibodies

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2, multicenter, open-label study of tislelizumab in patients with relapsed/refractory cHL. The primary efficacy endpoint is the overall response rate (ORR), defined as the proportion of patients who achieve a best response of complete response (CR) or partial response (PR) per the Lugano Classification and as determined by the investigator.

A total of approximately 42 patients with relapsed/refractory cHL will be enrolled into one of two cohorts based on prior therapies received: Cohort 1 will include patients who have failed to achieve a response or who have had disease progression after autologous hematopoietic stem cell transplantation (HSCT); Cohort 2 will include patients who have failed to achieve a response or who have had disease progression after at least 1 prior systemic regimen for cHL and are not candidates for autologous or allogeneic HSCT. The primary efficacy analysis will be performed for both cohorts combined, and subgroup analyses by cohorts will be performed.

All patients will receive tislelizumab 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or study withdrawal for other reasons. The end of the study is expected to occur up to approximately 2 years after enrollment of the last patient. Patients who remain on study treatment at the end of the study may have an opportunity to receive tislelizumab in a separate rollover or extension study or post-trial supply program.

Treatment with tislelizumab will be open label. Screening procedures must be performed within 28 days prior to the first dose of study treatment, unless noted otherwise. Once all screening assessments have been completed and study eligibility has been confirmed, study treatment must commence within 14 days of confirmation, which is within the 28-day screening window prior to the first dose of study treatment. Treatment will continue until disease progression, unacceptable toxicity, withdrawal of treatment consent, or study termination. Each cycle consists of 21 days. A schedule of efficacy and safety assessments is presented in Appendix 1.

Study Assessments

At screening, written informed consent and medical history will be collected, and eligibility based on inclusion and exclusion criteria will be determined. Baseline assessments will include pulmonary function test, hepatitis B and C serologies (and DNA levels, if necessary), and echocardiogram or multigated acquisition scan. HIV results will be recorded if previously known. Throughout the study, vital signs, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, complete blood count with differential, and serum chemistry panel will be monitored. Additional assessments will include height and weight, 12-lead electrocardiogram (ECG), erythrocyte sedimentation rate, pregnancy test (if applicable), and thyroid function evaluation.

Tumor assessments will be performed using PET-CT at screening, at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, and every 24 weeks (± 14 days) thereafter until disease progression. Computed tomography (CT) with contrast will be performed at screening and every 24 weeks starting from Cycle 1 Day 1 until disease progression. Patient-reported outcomes (European Quality of Life 5-Dimensions 5-Levels health questionnaire [EQ-5D-5L] and European

Organisation for Research and Treatment of Cancer Quality of Life cancer core questionnaire [EORTC QLQ-C30]) will also be assessed.

All patients should continue study assessments until disease progression is confirmed by the investigator, unacceptable toxicity, or withdrawal of consent, whichever comes first, or until the end of the study, which is expected to occur up to approximately 2 years after enrollment of the last patient. Patients who remain on study treatment at the end of the study may have an opportunity to receive tislelizumab in a separate rollover or extension study or post-trial supply program. Patients have the right to voluntarily withdraw from the study and the investigator has the right to discontinue a patient from study treatment at any time, including for a medical condition that may jeopardize the patient's safety. A patient in Cohort 2 who achieves complete remission and is otherwise a candidate for autologous HSCT may proceed to autologous HSCT at the discretion of the investigator and with approval from the sponsor, on condition that the reason that the patient was ineligible at screening to undergo HSCT is no longer applicable. The investigator should contact the sponsor to discuss autologous HSCT and tislelizumab maintenance therapy post-autologous HSCT.

Pharmacokinetic (PK) and immunogenicity analyses will be conducted. For biomarker analyses, archival and/or fresh tumor tissue samples will be collected.

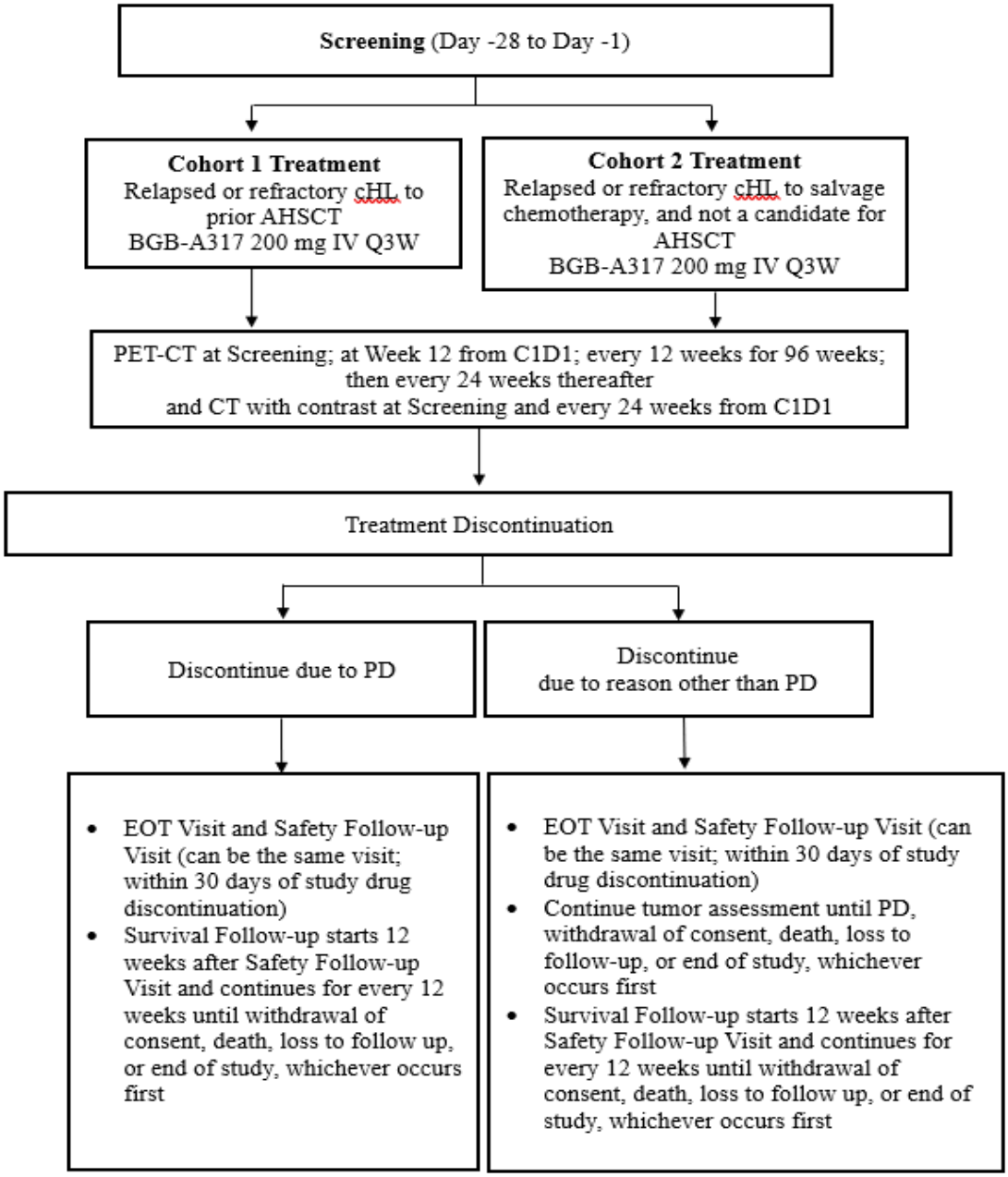
Safety assessments will include a review of adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, pulmonary and cardiac function tests, electrocardiograms, ECOG performance status, and vital signs. All AEs and laboratory safety measurements will be graded per the NCI-CTCAE v5.0.

A Safety Follow-up Visit will be mandatory. All AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last dose of study treatment. A Safety Monitoring Committee will review safety data after at least 20 patients have been on treatment for at least 9 weeks in order to determine if the proposed dosing schedule of tislelizumab is safe and tolerable.

The timing of all study procedures is provided in the Schedule of Assessments (Appendix 1). Figure 2 depicts the study design.

3.2. Study Schema

Figure 2: Study Design



Abbreviations: AHSCT: autologous hematopoietic stem cell transplant; C1D1: cycle 1 day 1; cHL: classical Hodgkin lymphoma; CT: computed tomography; EOT Visit: End-of-Treatment Visit; IV: intravenous; PD: progressive disease; PET-CT: positron emission tomography-computed tomography; Q3W: once every 3 weeks.

4. STUDY POPULATION

The specific eligibility criteria for enrollment into Cohort 1 and Cohort 2 are provided in Section 4.1 and Section 4.2, respectively. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Patients may be enrolled in the study only if they meet all of the following criteria:

1. Male or female ≥ 18 years of age at time of informed consent (or acceptable age according to local regulations, whichever is older)
2. Histologically confirmed diagnosis of relapsed or refractory cHL
3. Relapsed cHL (disease progression after PR or CR to the most recent therapy) or refractory cHL (failure to achieve PR or CR to most recent therapy). Patients will be allocated to 1 of 2 cohorts based on the following criteria:
   - Cohort 1: Relapsed or refractory to prior autologous HSCT
     - Has failed to achieve a response or has had disease progression after autologous HSCT.
     - Is not a candidate for additional autologous or allogeneic HSCT
   - Cohort 2: Relapsed or refractory to salvage chemotherapy, and has not received prior autologous or allogeneic HSCT
     - Has received at least 1 prior systemic regimen for cHL
     - Is not a candidate for autologous or allogeneic HSCT
4. Measurable disease defined as ≥ 1 FDG-avid nodal lesion that is > 1.5 cm in the longest diameter, or ≥ 1 FDG-avid extra-nodal lesion (eg, hepatic nodules) that is > 1 cm in the longest diameter
5. Able to provide fresh or archival tumor tissues (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 freshly cut, unstained FFPE slides) from an evaluable core or excisional biopsy with an associated pathological report
6. ECOG performance status of 0 or 1
7. Life expectancy ≥ 12 weeks
8. Adequate organ function, as indicated by the following laboratory values:
   - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L, independent of growth factor support within 7 days of first dose
   - Platelet ≥ 75 x 10^9/L, independent of transfusion, growth factor, or thrombopoietin receptor agonist support within 7 days of first dose
   - Hemoglobin (Hgb) ≥ 8 g/dL or ≥ 5 mmol/L
   - Creatinine clearance > 30 mL/min

- AST (SGOT) and ALT (SGPT) ≤ 2.5 x the ULN or ≤ 5 x ULN if liver lymphoma involvement is present
- Serum total bilirubin ≤ 1.5 x ULN (total bilirubin level < 4 x ULN for patients with Gilbert syndrome)

9. No evidence of dyspnea at rest and a pulse oximetry of > 92% while breathing room air
10. DLCO (adjusted for alveolar volume) > 60% of predicted value; FEV1 and FVC, FEV1/ FVC all > 50% predicted value
11. Female patients of childbearing potential must be willing to use a highly effective method of contraception for the duration of the study and for ≥ 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test within 7 days before the first dose of study drug. Please refer to Appendix 9 for a list of acceptable birth control/contraception methods and contraceptive guidelines
12. Males are eligible to enter and participate in the study if they have been vasectomized or if they agree to use barrier contraception with other highly effective methods as described in Appendix 9 during the study treatment period and for ≥ 120 days after the last dose of tislelizumab
13. Ability to provide written informed consent and can understand and comply with the requirements of the study

4.2. Exclusion Criteria

Patients will not be enrolled in the study if they meet any of the following criteria:

14. Nodular lymphocyte-predominant Hodgkin lymphoma or gray zone lymphoma
15. Prior allogeneic hematopoietic stem cell transplantation
16. History of severe hypersensitivity reaction to monoclonal antibodies
17. New York Heart Association (NYHA) class III or IV heart failure, unstable angina, severe uncontrolled ventricular arrhythmia, electrocardiographic evidence of acute ischemia, or myocardial infarction within 6 months of first day of screening
18. Prior malignancy within the past 3 years except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix, breast, or other site for which in situ carcinoma has metastatic potential
19. Prior therapy targeting PD-1, PD-L1, PD-L2, or CTLA-4 pathways
20. Has received:
    - Systemic chemotherapy, targeted small molecule therapy, or radiation therapy within 4 weeks prior to Cycle 1 Day 1
    - Recent treatment with another monoclonal antibody within 4 weeks prior to Cycle 1 Day 1
    - Investigational treatment or device within 4 weeks (or 5 half-lives, whichever is shorter) prior to Cycle 1 Day 1

- Or has not recovered from AEs (ie, ≤ Grade 1 or baseline level) due to prior therapy. (Note: Patients with alopecia or ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study if all other criteria are met)

21. Active autoimmune disease or history of autoimmune disease that may relapse (see Appendix 8)

    - Patients with the following are not excluded and may proceed to further screening: Vitiligo, eczema, type I diabetes mellitus, and endocrine deficiencies including thyroiditis managed with replacement hormone and/or physiologic corticosteroids
    - Patients with the following should be evaluated for the presence of target organ involvement and the potential need for systemic treatment, but should otherwise be eligible: Rheumatoid arthritis and/or other arthropathies, Sjögren's syndrome, or psoriasis controlled with topical medication, and patients with positive serology such as positive antinuclear antibody or anti-thyroid antibody

22. Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of the first dose of tislelizumab

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

    - Adrenal replacement doses of ≤ 10 mg daily prednisone equivalent in the absence of active autoimmune disease
    - Topical, ocular, intra-articular, intranasal, and inhalational corticosteroid (with minimal systemic absorption)
    - A brief course of corticosteroid for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen)

23. History of interstitial lung disease or noninfectious pneumonitis or has evidence of interstitial lung disease or noninfectious pneumonitis
24. Serious acute or chronic infection requiring systemic therapy
25. Known central nervous system (CNS) lymphoma
26. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs
27. Known history of infection with HIV, human T-cell lymphotropic virus-1, or human T-cell lymphotropic virus-2
28. Serologic status reflecting active hepatitis B or C infection as follows:

    - Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible only if hepatitis B virus (HBV) DNA is undetectable by an assay with sensitivity ≤ 20 IU/mL. If so, patients may either undergo regularly scheduled monitoring of HBV DNA or less frequent monitoring of HBV DNA while on prophylactic antiviral medication as defined by regional standard of care.

- Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible only if HCV RNA is undetectable.

29. Autologous hematopoietic stem cell transplantation within 100 days of first dose of tislelizumab
30. CAR-T therapy within 12 months prior to the first dose of study drug
31. Use of any live vaccine against infectious diseases (eg, influenza, varicella, etc) within 4 weeks (28 days) of the first dose of tislelizumab, and any intended use within 60 days after the last dose of tislelizumab
32. Major surgery within 4 weeks of the first dose of tislelizumab
33. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment
34. Has hypersensitivity to tislelizumab or any of its excipients
35. Concurrent participation in another therapeutic clinical trial

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

See the Pharmacy Manual for detailed information regarding product preparation, administration, accountability, and disposal.

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous injection in a single-use glass vial containing a total of 100 mg 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 in a single-carton box.

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

Tislelizumab (investigational product) will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Only patients enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with investigational product-specific requirements. The investigational product must be kept at 2°C to 8°C (36°F to 46°F) and protected from light.

5.2. Dosage, Administration, and Compliance

See the Pharmacy Manual for detailed information regarding product preparation, administration, accountability, and disposal.

5.2.1. Tislelizumab

Patients will receive tislelizumab at 200 mg intravenously once every 3 weeks. One cycle is 21 days. The minimum amount of time between doses is 10 days. Patients should not receive premedication to prevent an infusion reaction before the first infusion of tislelizumab in order to determine whether premedication is necessary. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days. The premedication should be chosen per institutional standard of care, at the discretion of the treating physician.

Tislelizumab 200 mg will be administered by intravenous infusion. It is recommended to use a volumetric pump through an intravenous line containing a sterile, nonpyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter. A pump may not be required if infusion speed can be controlled through alternative means and consistent with approved institutional procedures. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, patients who receive the first and second infusion of tislelizumab must be observed for 2 hours after infusion. From Cycle 3 onward, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents. Resuscitation equipment and emergency agents need to be available.

The initial infusion will be delivered over 60 minutes. If the 60-minute infusion is tolerated, each subsequent infusion may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

Guidelines for treatment interruption or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Appendix 6 and Section 8.7.1, respectively.

Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.3. Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate electronic case report form (eCRF). AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.4. Dose Interruption, Modification, or Delays

Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.4.1. Dose Modification for Tislelizumab

There will be no dose reduction of tislelizumab in this study. Dose delays of < 12 weeks will be permitted. The investigator should make every effort to maintain dose intensity in patients.

Patients may temporarily suspend study treatment if they experience a toxicity that is considered related to tislelizumab and requires that a dose be withheld. Patients should resume tislelizumab treatment as soon as possible after the AE recovers to baseline or Grade 1 severity (whichever is more severe), unless the AE is a hematologic toxicity as described below, within 12 weeks after the last dose of tislelizumab. If the patient is unable to resume tislelizumab in that timeframe, study treatment should be discontinued.

In case a patient is benefiting from the study treatment while meeting the discontinuation criteria, resumption of study treatment may occur upon discussion and agreement with the sponsor medical monitor.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (refer to the visit window in Appendix 1), with subsequent dosing rescheduled according to the planned schedule every 3 weeks.

Dose administration of tislelizumab will be held in the event of the following hematologic toxicity(s) if assessed as related to study drug and not due to underlying lymphoma:

- Grade 4 anemia
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with bleeding
- Grade 4 neutropenia
- Grade 3 febrile neutropenia

If hematologic toxicity is considered to be immune-related, refer to Appendix 6 for specific guidance on management, dose modification and discontinuation criteria.

In general and if not considered to be immune-related, dosing may resume upon recovery of cytopenia(s) to at least Grade 2 or better and within 12 weeks after the last dose of tislelizumab. If the patient is unable to resume tislelizumab in that timeframe, study treatment will be discontinued.

For potential cases of Hy's Law, defined as ALT or AST >3X ULN and total bilirubin >2X ULN in the absence of initial findings of cholestasis or other reason(s) (eg, concomitant disease or medication, liver involvement of disease, etc) for concurrent increased AST or ALT and total bilirubin, discontinue study treatment. Obtain hepatology consultation and manage per local institutional guidance.

Dose administration of tislelizumab will be held temporarily until resolution or improvement in the event of the following immune-related toxicity(s) if assessed as related to study drug and not due to underlying lymphoma:

- Grade 2 hepatitis
- Grade 2 to 3 skin reaction(s), dermatitis

Dose administration of tislelizumab will be permanently discontinued in the event of the following immune-related toxicity(s) if assessed as related to study drug and not due to underlying lymphoma:

- Grade 3 to 4 hepatitis
- Grade 4 skin reaction(s), dermatitis
- Stevens-Johnson syndrome or toxic epidermal necrolysis
- Guillain-Barré syndrome

Management guidelines for irAEs and infusion-related reactions in patients treated with tislelizumab are described in Appendix 6 and Section 8.7.1, respectively.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

Permitted and excluded prior therapies are outlined in the inclusion and exclusion criteria (Section 4.1 and Section 4.2).

6.2. Concomitant Therapy

6.2.1. Permitted Medications

In general, concomitant medications and therapies deemed necessary for supportive care (eg, antiemetics, antidiarrheals) and safety of the patient are allowed. All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the eCRF, including all prescription and over-the-counter medications, and intravenous medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF. All concomitant medications received within 28 days before the first dose of study medication and 90 days after the last dose of study medication should be recorded.

Systemic corticosteroids may be used for the control of irAEs as detailed in the most current American Society of Clinical Oncology (ASCO) Practice Guideline for the management of irAEs in patients treated with immune checkpoint inhibitor therapy (Brahmer et al 2018).

Patients may continue to receive hormone replacement if initiated prior to enrollment.

Transfusions and growth factors can be administered to mitigate immune related neutropenia and thrombocytopenia while on study treatment.

6.2.2. Prohibited Medications

The following medications are prohibited during screening and treatment periods:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroid > 10 mg daily prednisone equivalent (except to treat a drug-related AE) or requirement of prolonged corticosteroid treatment (ie, >12 weeks) for the treatment of a drug-related AE, including an irAE. Patients who require prolonged corticosteroid treatment of >12 weeks for a drug-related AE must permanently discontinue from study therapy.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, standard or investigational agents for treatment of cancer)
- Live vaccines within 28 days prior to the first dose of study drug and while participating in the study. Examples of live vaccines include, but are not limited to, measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, bacille Calmette-Guerin (BCG), and typhoid vaccine. Inactivated influenza vaccine is allowed.

7. STUDY ASSESSMENTS AND PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 1).

Visit Windows

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 7 days (ie, 7 days before or after the given day) unless otherwise stated in the Schedule of Assessments. The minimum amount of time between doses is 10 days. Study drug supplies must be taken into account when scheduling visits during windows. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

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 prior to study treatment infusion unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (see Appendix 1), with subsequent visits conducted according to the planned schedule of every 3 weeks.

7.1. Screening

7.1.1. Informed Consent

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the informed consent form will be given to the patient to read, and the patient must have adequate time to understand the content and ask questions.

Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and the informed consent process must be documented in the patient's clinical record. Informed consent may be obtained before the 28-day screening period. Consent must be obtained using the most current version of the form approved by the Independent Ethics Committee.

All screening procedures must be performed within 28 days prior to the first dose of study drug, unless noted otherwise; assessments not completed within this interval must be repeated. Once all screening assessments have been completed and study eligibility has been confirmed, study treatment must commence within 14 days of confirmation, which is within the 28-day screening window prior to the first dose of study treatment. Results of standard-of-care tests or examinations for echocardiogram/multigated acquisition scan performed prior to obtaining informed consent and ≤ 90 days prior to enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests, subject to review and agreement by the medical monitor or designee. Repeating screening procedures or tests is allowed if the patient did not previously meet the inclusion and exclusion criteria or if needed to have a documented result within the protocol-specified screening window.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before enrollment, study site personnel should document the screen failure in the patient's source documents. The documentation should include demographics and medical history, the reason for screen failure, the eligibility criteria reviewed, procedures performed, etc.

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 9 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

7.1.3. Medical and Cancer History

All medical and cancer history will be reviewed after informed consent has been obtained, including the presence or absence of disease-related constitutional symptoms. Clinically significant medical history (ie, previous diagnoses, diseases, or surgeries) that does not pertain to the study indication but started before signing the informed consent and considered relevant to the patient's study eligibility will be collected and captured in the eCRF. "Clinically significant" is defined as any event, diagnosis, or laboratory value requiring treatment or follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

Other background information to be collected include history of cHL (including the date of initial diagnosis and current disease status), staging, sites of disease, International Prognostic Score (Appendix 3), and presence or absence of disease-related constitutional symptoms. Prior medications/significant nondrug therapies will also be collected. Demographic factors such as age, gender, race, and ethnicity could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and ethnicity data are collected in accordance with International Council for Harmonisation (ICH) guidance (ICH E5 1998, ICH E17 2017) adopted by the European Medicines Agency (EMA) and US FDA, to understand whether race/ethnicity could influence the PK, safety, and/or efficacy of the study drug. For example, population PK analysis is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Such variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications), and can lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from race/ethnicity and other demographic analyses will be incorporated into drug product labeling to provide guidance on safety and efficacy variations (if any) linked to certain populations (eg, race or ethnic group) as well any potential dose adjustment needed for those populations. Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety, and/or efficacy.

Nonserious AEs will be recorded during the screening period as medical history.

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. All screening procedure results, and relevant medical history must be available before eligibility can be determined. All

inclusion criteria must be met and none of the exclusion criteria may apply. No eligibility waivers will be granted.

In France, for any patient enrolling to Cohort 1 who has not received prior brentuximab vedotin and chemotherapy regimen, the investigator must document rationale for tislelizumab administration in the medical record. This is required by the French Health Authority, Agence nationale de sécurité du médicament et des produits de santé (ANSM).

For sites in countries where BeiGene is the sponsor, after a patient is screened and the investigator determines that the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and send it, via secure transmission, to the medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that the final Eligibility Authorization Packet is in the patient's file before proceeding with study procedures.

For all sites, either unstained tissue (block or unstained slides) or stained slides, together with pathology report, should be sent to a central pathology laboratory for confirmation of tissue diagnosis. If unstained tissue (block or unstained slides) or stained slides are not available, collection of a fresh tumor biopsy at screening is mandatory. Central pathology confirmation is not required prior to enrollment. If an archival tissue sample is available, it should be collected for central pathology and other biomarker analysis. Refer to Section 7.9 for details.

7.2.2. Patient Numbering

Patients will be identified by a patient number. Each patient enrolled in this study will receive a unique patient number that will be assigned when the patient is screened or enrolled in the study. Patient numbers will be assigned by the EDC tool 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.

7.3. Study Drug Dispensation

Tislelizumab will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

Safety assessments should be performed by the investigator at all visits throughout the study. Safety assessments include monitoring of all AEs and SAEs, regular monitoring of blood tests, vital signs, weight, and performance status, and regular physical examinations. For the schedule of study visits, see the Schedule of Assessments (Appendix 1).

7.4.1. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of (1) head, eyes, ears, nose, throat, (2) cardiovascular, (3) dermatological, (4) musculoskeletal, (5) respiratory, (6) gastrointestinal, and (7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the eCRF with appropriate disease/condition terms. Height (baseline only) and weight will be measured and recorded in the eCRF.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. See Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.2. Vital Signs Assessment

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

7.4.3. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status (Appendix 7) will be assessed during the study.

7.4.4. Pulmonary Function Tests

Pulmonary function tests include spirometry and lung diffusion capacity. Screening evaluations must be performed within 28 days prior to first dose of tislelizumab. Pulmonary function tests can also be performed when clinically indicated at the discretion of the investigator during the study.

7.4.5. Electrocardiogram and Cardiac Function Tests

ECG assessments are to be performed with the patient in a semi-recumbent or supine position and rested for at least 5 minutes.

Cardiac function is assessed by either echocardiography or multigated acquisition scan. Screening evaluations may be performed within 90 days prior to enrollment, subject to review and agreement by the medical monitor or designee. ECG can also be performed when clinically indicated at the discretion of the investigator during the study.

7.4.6. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE v5.0. Characterization of toxicities will include severity, duration, outcome, and time to onset. All AEs, including SAEs, will be collected as described in Section 8.

7.4.7. Concomitant Medications Review

Any new medications, changes in ongoing medications or procedures, and medications discontinued within 28 days before the first visit in Cycle 1 and since the prior study visit, thereafter, will be recorded.

7.5. Tumor Assessments

7.5.1. Imaging Studies

Response assessments will be by PET-CT and CT with contrast and categorized as per the Lugano Classification (Appendix 4). Total body magnetic resonance imaging (MRI) is allowed if CT with contrast is contraindicated. At time points in which a CT scan with contrast is required, PET-CT may be adequate if the CT portion of the PET-CT is of diagnostic quality and contrast is

administered. Because PET-CT is considered to be the standard imaging modality for response assessment in HL as per the Lugano guidelines (Cheson et al 2014), when both PET-CT and CT are performed but results are discordant, overall response will generally be defined by PET-CT.

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. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed per the originally planned schedule.

Imaging data may be uploaded to a central database for future review.

7.5.1.1. PET-CT

As per the Lugano guidelines (Cheson et al 2014), PET-CT is considered the standard imaging modality for response assessment in HL. Tumor assessment by PET-CT will be performed at screening, at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, and then every 24 weeks thereafter until disease progression (Appendix 1).

A banking of the PET-CT scans is mandatory and will be organized for this study. For each patient when applicable, PET-CT will be uploaded to the imaging platform.

7.5.1.2. CT With Contrast

Tumor assessment by CT with contrast of neck, chest, abdomen, and pelvis will be performed at screening and every 24 weeks starting from Cycle 1 Day 1 until disease progression. Total body MRI or CT without contrast of the chest plus MRI of the neck, abdomen, and pelvis is allowed if CT with contrast is contraindicated. At time points in which a CT scan with contrast is required, PET-CT may be adequate if the CT portion of the PET-CT is of diagnostic quality and contrast is administered.

Thickness of CT scan slice should not exceed 8 mm cuts using a contiguous reconstruction algorithm.

Banking of the CT scans is mandatory and will be organized for this study. For each patient, CT scans will be uploaded to the imaging platform, when applicable.

7.5.2. Disease Progression With Immune Checkpoint Inhibitors

During treatment with immune checkpoint inhibitors such as tislelizumab, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by the apparent increase of existing tumor masses or appearance of new tumor lesions. Patients are allowed to continue study treatment if there is suspicion of pseudo-progression, provided they are asymptomatic and have radiographic progression only, until follow-up imaging and/or biopsy demonstrates progressive disease, at which time study treatment will be discontinued permanently.

If appropriate, the medical monitor may consult with the investigator (or vice versa) to review cases of potential pseudo-progression and determine if it is in the best interest of the patient to continue study treatment.

7.6. Laboratory Assessments

Laboratory tests will be collected and analyzed as specified in Appendix 1. Screening blood tests performed within 3 days before the first study drug administration do not need to be repeated on Cycle 1 Day 1. Abnormal laboratory values will be considered AEs only if they are associated with clinical signs or symptoms that are clinically significant and/or require therapy and should be recorded on the AE eCRF. In addition, isolated abnormal laboratory values that are considered clinically significant (eg, any event, diagnosis, or laboratory value requiring treatment or follow-up or the presence of signs or symptoms that require medical intervention) should be recorded on the AE eCRF. Local laboratory assessments of serum chemistry and hematology will be conducted, of which certain elements will be collected as specified in Appendix 2.

7.6.1. Hematology

Hematology laboratory studies include white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, basophil), hemoglobin, hematocrit, and platelet count. In the event of ≥ Grade 3 neutropenia or thrombocytopenia that develops during study treatment, complete blood count monitoring will be conducted as often as clinically indicated per the investigator's medical judgment to ensure patient safety. Close monitoring should occur until the toxicity resolves to ≤ Grade 2. Refer to Section 5.4 for dose modification of tislelizumab due to hematologic toxicity(s).

7.6.2. Clinical Chemistry

Clinical chemistry includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen (if available), creatinine, glucose, calcium, magnesium, phosphorus, albumin, AST, ALT, total bilirubin, conjugated bilirubin, alkaline phosphatase, lactate dehydrogenase, total protein, uric acid, creatine kinase, and creatine kinase-cardiac muscle isoenzyme. In the event that creatine kinase-cardiac muscle isoenzyme fractionation is not available, troponin I and/or troponin T will be assessed instead. In the event a ≥ Grade 3 clinical chemistry toxicity develops during study treatment, the frequency of clinical chemistry monitoring will be conducted as often as clinically indicated per the investigator's medical judgment to ensure patient safety. Close monitoring should occur until the toxicity resolves to ≤ Grade 2.

7.6.3. Hepatitis B and Hepatitis C Testing

These hepatitis B/C serologic markers and/or viral load will be tested at screening:

- HBsAg, antibodies against HBsAg (HBsAb), antibodies against hepatitis B core antigen (HBcAb)
- HCV serology (anti-HCV)
- HBV DNA and HCV RNA

Hepatitis B testing includes HBsAg, HBcAb, and HBsAb, as well as HBV DNA by polymerase chain reaction (PCR) if the patient is negative for HBsAg, but positive for HBcAb (regardless of HBsAb status).

Hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is positive for HCV antibody.

Patients who have detectable levels of HCV RNA (≥ 15 IU/mL) are not eligible. Patients who are positive for HBsAg and/or detectable HBV DNA are not eligible.

Patients who are negative for HBsAg (required for study eligibility) and positive for HBcAb should have HBV DNA testing performed. If HBV DNA is detectable by an assay with a sensitivity of ≤ 20 IU/mL, the patient is not eligible for the study. If HBV DNA is not detected, patients may elect to:

- Undergo HBV DNA testing by PCR every other cycle beginning in Cycle 2 (ie, Cycles 2, 4, 6, 8, etc.) without beginning prophylactic antiviral medication, OR
- Begin prophylactic dosing of antiviral therapy according to the regional standard of care. Patients will undergo HBV DNA testing by PCR every 4 cycles beginning in Cycle 4 (ie, Cycles 4, 8, 12, etc.). Medications recommended and excluded are described in Section 6. It is recommended that antiviral therapy be initiated at least 2 weeks before the first dose of study treatment and continue until 6 months after discontinuation of study treatment. Patients may enter the study on HBV antiviral medication according to the regional standard of care.

If HBV DNA is detectable at any time during the study, tislelizumab will be held until antiviral therapy is administered according to the regional standard of care. Resumption of study drug in patients whose HBV reactivation resolves (ie, HBV DNA is undetectable) should be discussed with and approved by physicians with expertise in managing hepatitis B and the medical monitor.

Patients positive for HCV antibody but negative for HCV RNA (< 15 IU/mL) must undergo HCV RNA screening every other cycle, beginning in Cycle 2 (ie, Cycles 2, 4, 6, 8, etc.). Patients with detected HCV RNA should stop study drug and antiviral therapy should be initiated.

Patients at risk for reactivation will also have HBV DNA and/or HCV RNA testing performed at the Safety Follow-up Visit.

The medical monitor should be informed of any suspected hepatitis B or hepatitis C reactivation.

Table 1 shows how the results for HBV/HCV and HBV/HCV testing at screening relate to inclusion and exclusion criteria.

Table 1: Active Hepatitis B Virus or Hepatitis C Virus Infection (Detected Positive by Polymerase Chain Reaction)

Screening Assessment	Meets Inclusion Criteria	To be Excluded
HBV	**HBsAg (-) and HBcAb (-)**	**HBsAg (+)**
	HBsAg (-) *and* HBcAb (+) *HBV DNA undetectable by an assay with sensitivity ≤ 20 IU/mL and either of the following:* *Perform monitoring of HBV DNA (HBV DNA screening by PCR every other cycle, beginning in Cycle 2)* OR *Antiviral therapy administered and perform monitoring of HBV DNA (HBV DNA screening by PCR every 4 cycles, beginning in Cycle 4)*	**HBsAg (-) *and* HBcAb (+)** *HBV DNA Detected*
HCV	**Antibody (-) *or* Antibody (+)** *HCV RNA "Not-detected" (<15 IU/mL)* *Perform monitoring of HCV RNA every other cycle, beginning in Cycle 2*	**Antibody (+)** *HCV RNA Detected*

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction.

7.6.4. Thyroid Function Test

Evaluations of free triiodothyronine (T3), free thyroxine (T4), and thyroid-stimulating hormone will be performed as specified in Appendix 1.

7.6.5. Liver Function Tests

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, and conjugated bilirubin will be performed locally. Assessments should be as indicated in Appendix 1.

7.6.6. Pancreatic Enzymes

Pancreatic enzymes (amylase and lipase) will be tested locally if clinically indicated while on treatment. Assessments should be as indicated in Appendix 1.

7.6.7. Pregnancy Test

For women of childbearing potential, a serum pregnancy test will be performed at screening no more than 7 days before the first study drug administration. Any female patient who is pregnant

will not be eligible for the study. Urine pregnancy tests will be performed locally on Day 1 of every cycle starting with Cycle 2. Pregnancy tests must be continued during every cycle for at least 30 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Serum pregnancy tests may be substituted for urine pregnancy tests if the site is not able to perform urine testing. A patient who has a positive pregnancy test result at any time after administration of the study drug will be immediately withdrawn from participation in the study.

7.7. Pharmacokinetics

The PK of tislelizumab will be characterized in this study. Blood samples will be collected from all patients at the time points described in Appendix 1. The time of study drug administration and actual PK collection time must be recorded on the eCRF. The actual time each sample is collected will be captured to the nearest minute in the eCRF and recorded in the database. Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma tislelizumab concentrations using a validated method.

Shipping, storage, and handling of samples for the assessment of tislelizumab PK assays will be managed through a central laboratory. Serum samples will be tested for tislelizumab concentration using a validated immunoassay. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.8. Antidrug Antibody Evaluation Procedures

Tislelizumab might elicit an immune response, so patients with signs of any potential immune response to tislelizumab will be closely monitored for the development of antidrug antibody (ADA) during this study.

Blood samples will be collected from all patients at the time points described in Appendix 1. Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study. Samples will be shipped to the designated bioanalytical laboratory for quantification of plasma tislelizumab concentrations using a validated method.

Shipping, storage, and handling of samples for the assessment of tislelizumab ADAs will be managed through a central laboratory. Serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay. Instruction manuals and supply kits will be provided for all central laboratory assessments.

The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Bai et al 2012; Worobec and Rosenberg 2004) to characterize ADA responses to tislelizumab in support of the clinical development program.

7.9. Biomarkers

Tissue and optional blood samples for biomarker assessment will be collected as stated in Appendix 1. Shipping, storage, and handling of blood, archival tumor, fresh tumor, and tumor tissue for the assessment of biomarkers will be managed through a central laboratory. See the Laboratory Manual for sample handling details.

Archival tumor tissue (FFPE blocks or approximately 15 unstained slides) must be sent to a central laboratory for diagnosis confirmation and biomarker analysis, including but not limited to immunohistochemistry assay and/or fluorescence in situ hybridization to detect status of PD-L1, CD64, MHC II and other proteins related to disease or treatment mechanism, presence of immune cells in the tumor microenvironment, PD-L1/PD-L2 gene alteration, EBV infection status, etc. Gene mutation profiling and/or immune-related gene-expression profiling, and tumor-infiltrating immune cells that are related to response or clinical benefit of tislelizumab may also be evaluated. Tumor tissue submission is mandatory for all patients who consent to participate in the study, and an additional fresh baseline tumor biopsy (optional) at screening is strongly recommended. If a biopsy is not performed at screening, a sample of archival tumor tissue should be submitted from the confirmation of any relapse, with the most recent relapse sample being preferred. If tissue from a relapse is unavailable, archival tissue from the initial diagnosis may be submitted.

An optional tumor biopsy will be taken from accessible tumor sites at the time of PR to explore tumor biomarkers of tislelizumab response and resistance. For patients who have confirmed disease progression during the study, optional biopsies will also be taken to explore resistance mechanisms. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the screening biopsy. Written patient consent is required prior to collecting a fresh tumor biopsy sample.

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. 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.

Optional blood samples will be taken at screening, at Weeks 3, 6, 12, 24, 48, and at the time of disease progression or 6 months after treatment to explore the association of blood-based biomarkers (such as ctDNA, cytokine, immune cell profiling, etc.) with response, resistance, and prognosis to tislelizumab. Written patient consent is required for blood sample collections.

7.9.1. Archival Tissue Collection for Central Confirmation of Diagnosis and Biomarker Analysis

Archival tumor tissue (FFPE blocks or approximately 15 unstained slides) will be collected at the Screening Visit and sent to a central laboratory for central confirmation of diagnosis and biomarker analysis. Central review of the tissue will be performed to confirm diagnosis of cHL (central confirmation of cHL diagnosis is not required for study entry). Enrollment will not be increased based on central review of pathology as patients will not be replaced in this study.

7.10. Patient-Reported Outcomes

Patient-reported outcomes will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients in both cohorts will be asked to complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedule of Assessments (Appendix 1) before study drug is administered.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The EuroQol Group 1990, Herdman et al 2011). Patients will self rate their current state of mobility, self care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine". A sample questionnaire is provided in Appendix 10 as an example only.

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients (Fayers et al 2001). It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. The EORTC QLQ-C30 includes 30 separate questions (items). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in non-Hodgkin lymphoma patients. It is a reliable and valid measure of PRO in cancer patients and takes about 11 minutes to administer. A sample questionnaire is provided in Appendix 11 as an example only.

7.11. End of Treatment

All patients, regardless of reason for discontinuation of study treatment, will undergo an End-of-Treatment (EOT) Visit within 30 days (+ 7 days) of stopping study drug. This visit may be considered the Safety Follow-up Visit. The reason for discontinuation from treatment will be recorded on the eCRF. Section 7.13.1 describes the circumstances under which patients may discontinue study drug.

Patients may voluntarily withdraw consent from the study at any time and may continue to participate in follow up, even if they withdraw consent from study treatment.

See the Schedule of Assessments (Appendix 1) for further details.

7.12. Follow-up Period

All patients who discontinue treatment for any reason will be required to comply with the safety, efficacy, and survival follow-up assessments specified in Appendix 1.

7.12.1. Safety Follow-up

Patients who discontinue treatment for any reason will be asked to return to the clinic for a Safety Follow-up Visit (to occur within 30 days [+ 7 days]) after the last dose of study drug. In addition, telephone contacts (or clinic visit, if preferred) with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or a new anti-lymphoma therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab. All AEs and SAEs are collected up to 90 days after the last dose of study drug. Beyond 90 days, investigators should continue to report any SAEs that are believed to be related to study drug if they become aware of them.

Patients who discontinue study treatment prior to PD will continue to have their tumors assessed as outlined in Section 7.5.

7.12.2. Efficacy Follow-up

For patients who discontinue from study drug for any reason other than PD (eg, AE), disease status will be assessed radiographically by the same imaging modality used during study treatment. Tumor imaging, physical examination, and complete blood count (CBC) will be performed per protocol until disease progression, withdrawal of consent, death, loss to follow-up, or end of study, whichever occurs first.

7.12.3. Survival Follow-up

Patients will be followed for survival and further anti-lymphoma therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 90 days (± 14 days) after the Safety Follow-up Visit or as directed by the sponsor until withdrawal of consent, death, loss to follow-up, or end of study, whichever occurs first.

7.13. Discontinuation From Study Treatment or From the Study

7.13.1. Patient Discontinuation From Study Treatment

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 disease progression should be followed for tumor assessments (Section 7.5), safety (Section 7.12.1), and survival (Section 7.12.3), if possible.

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

- Disease progression
- AE(s)
- Patient withdrawal of consent
- Investigator decision
- Other, including pregnancy, patient noncompliance, and 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

7.13.2. 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

- Loss to follow-up
- Study closure

Premature discontinuation from the study (including all follow-up visits) will occur under the following circumstances:

- Major protocol deviations
- Patient withdrawal of consent
- Loss to follow-up
- Death
- Study termination by sponsor
- Investigator's discretion

Patients may voluntarily withdraw consent from the study at any time.

Patients lost to follow-up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should document, in the source documents, steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc.).

7.14. End of Study

The end of the study is expected to occur up to approximately 2 years after enrollment of the last patient. Patients who remain on study treatment at the end of the study may have an opportunity to receive tislelizumab in a separate rollover or extension study or post-trial supply program.

The sponsors have the right to terminate this study at any time. Reasons for early termination of the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients (refer to Section 9.4.2 for the study safety stopping criteria)
- Overall patient enrollment is unsatisfactory

The sponsors will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for a final visit. Assessments performed should include those required for the Safety Follow-up.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator or sponsors will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

The sponsors have the right to close a site at any time. The site will be notified of this decision in advance. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate, untimely, or incomplete data recording

- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, all patients have completed all study related assessments and all obligations have been fulfilled)

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. Limited safety data are available in patients and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and 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 immune-related AEs (irAEs), specifically the induction or enhancement of autoimmune conditions. The irAEs observed with anti-PD-1 therapy are presented in Section 8.7.3.

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

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with 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 viral vaccine within 28 days before first dose of study drug are excluded from the study. (See Section 4.2 for the full list of exclusion criteria.)

8.2.2. Safety Monitoring Plan

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

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

Serum samples will be drawn for determination of ADAs to tislelizumab in all patients. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2.1).

All AEs will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 90 days after the last dose of study drug(s). At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline level or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

Immune-related AEs will be recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, or duration, and/or has an association with a significantly worse outcome
- New condition(s) detected or diagnosed after study drug administration even though it may 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 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 prior to submission to the sponsor.

8.3.2. Assessment of Severity

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

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

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

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

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug 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 should be considered and investigated. The investigator should consult the Tislelizumab Investigator's Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every SAE prior to transmission of the SAE report to the sponsor, since causality assessment is 1 of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality after considering follow-up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (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

- Biological plausibility

An AE should be considered "related" to study drug 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). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Following 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 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 post-mortem findings, including histopathology.

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

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry or 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 judgement of the investigator. In general, clinically significant findings are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or

- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or
- require further diagnostic investigation.

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Planned hospital admissions or surgical procedures for an illness or disease which existed before the patient was enrolled in the study or before study drug was given are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier than planned)
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations

- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Tislelizumab Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after last dose of study treatment or until initiation of new anticancer therapy. For patients who begin new anticancer therapy, only irAEs will be reported during the 90-day period after the last dose of study treatment. Clinical symptoms that are determined by the investigator to be clearly due to disease progression and are not considered serious in nature should not be reported as AEs. The symptoms, signs, or clinical sequelae, if considered serious in nature, that result from disease progression should be reported as SAE term(s). Further, after this period, the investigator should report any SAEs that are assessed as related to tislelizumab treatment, at any time after treatment discontinuation.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 2.

Table 2: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time Frame for Making Initial Report	Documentation Method	Time Frame for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 h of first knowledge of the SAE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form

Abbreviations: h, hours; SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product 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 Institutional Review Board/Independent Ethics Committee (IRB/IEC).

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

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her Institutional Review Board or Independent Ethics Committee. The investigator should place copies of safety reports from the sponsor in the Investigator Site File.

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs or clinical sequelae, if considered serious in nature that result from disease progression should be reported as SAE term(s). However, clinical symptoms that are determined by the investigator to be clearly due to disease progression and are not considered serious in nature

should not be reported as AEs. If the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, then the term(s) should be reported as AE(s) or SAE(s) accordingly.

For instance, if a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression."

8.6.5. Deaths

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

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab, a pregnancy report form is required to 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 be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

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

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, Institutional Review Boards, and Independent Ethics Committees 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 document:

- Tislelizumab Investigator's Brochure

8.6.8. Assessing and Recording Immune-Related Adverse Events

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

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

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

8.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 2 hours afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a minimum of a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The management of infusion-related reactions, severe hypersensitivity reactions, and irAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drug is provided in Table 3.

Table 3: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
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, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. 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 below. The patient should be withdrawn from study drug(s) treatment.

Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: h, hours; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab 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 IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they 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 IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If a hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (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 immediately stopped and the patient discontinued from the study. Such reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm (which 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 patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and 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, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drug(s) infusion. Alternative treatments for fever (ie, paracetamol) may be given to patients at the discretion of the investigator.

Tumor Lysis Syndrome

Patients with a high tumor burden (presence of a leukemic phase, multiple organ involvement, or marrow infiltration) are recommended to receive prophylaxis for tumor lysis syndrome prior to the initiation of study treatment. These patients must be well hydrated. It is desirable to maintain a fluid intake of approximately 3 L/day, 1 to 2 days before the first dose of tislelizumab. All such patients with high tumor burden must be treated with a xanthine oxidase inhibitor (allopurinol) of > 300 mg/day orally. It is recommended that patients of Asian descent have HLA-B5801 testing before allopurinol therapy. If testing is not available, febuxostat 80 mg/day may be used or a suitable alternative treatment (eg, rasburicase) starting at least 12 to 24 hours prior to the first dose of tislelizumab. Patients should continue to receive prophylaxis with a xanthine oxidase inhibitor and adequate hydration prior to each infusion of tislelizumab, if deemed appropriate by the investigator.

Cytokine Release Syndrome

Although infrequent in incidence, cytokine release syndrome (CRS) has been observed in cancer patients treated with PD-1 checkpoint inhibitors (Chen et al 2017; Rotz et al 2017). Representing a constellation of inflammatory reactions that result from cytokine elevations associated with T-cell engagement and activation, patients with cytokine release syndrome may present with symptoms that include sepsis, fever, tachycardia, hypotension, coagulopathies, and deranged liver function tests. Often these symptoms can mimic disease progression or infection.

If CRS is suspected, patients should undergo evaluation as soon as possible. If needed, in-patient admission is recommended to fully evaluate patients for CRS as well as rule out infection, which can exacerbate CRS. Patients with a suspected infection should be aggressively treated with antibiotics and antifungal medication as needed. Serum ferritin, IL-6, CRP, LDH, and procalcitonin (Maakaron et al 2018) can be valuable tests in this setting.

Patients should be managed appropriately according to local institutional standard of care. The recommended treatment for CRS typically includes high-dose corticosteroids, use of the IL-6 inhibitor tocilizumab, and intensive supportive care. A thorough benefit-risk evaluation should be made by the investigator on the possibility of rechallenge with study treatment for patients who experience severe CRS and subsequently recover. Although there have been anecdotal reports of response to PD-1 inhibitors after rechallenge in extranodal natural killer/T-cell lymphoma (ENKL) patients with drug-induced CRS, the decision to resume study treatment should be weighed against a variety of factors and may involve consultation with additional specialists and also informing the medical monitor.

8.7.3. Immune-Related Adverse Events

Immune-related AEs (irAEs) 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, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but are not limited to serologic, immunologic, and histologic (biopsy) data. The irAE indicator on the eCRF AE page should be checked if alternative causes of the irAE have been ruled out; the irAE required the use of systemic steroids, other immunosuppressants, or endocrine therapy; and the irAE is consistent with an immune-mediated mechanism of action.

A list of potential irAEs is shown in Table 4. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on European Society for Medical Oncology (ESMO) and ASCO guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-related toxicities are detailed in Appendix 6. For any AEs not included in Appendix 6, see the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 4: Immune-Related Adverse Events

Body System Affected	Examples of Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's 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, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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

Recommendations for managing irAEs are detailed in Appendix 6.

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 with rechallenge should permanently discontinue treatment.

8.7.4. Recording Diagnosis Versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only "hepatitis" rather than "elevated transaminases," "bilirubin," or "jaundice").

However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable).

8.7.5. Recording Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (eg, clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report, if applicable). However, if a patient initially has a nonserious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the nonserious AE should be recorded as the start date of the nonserious AE. The onset date of the SAE should be recorded as the date that the nonserious AE became serious (eg, due to hospital admission).

8.7.6. Recording Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously without resolution between patient evaluation time points. Such AEs should be recorded only once on the AE eCRF (and SAE report, if applicable). If an AE worsens in grade, with the exception of an AE that is related and requires dose modification (ie, treatment discontinuation or dose interruption/delay), the worst grade should be recorded for the entire event. A persistent AE that is related and requires dose modification should be recorded separately on the eCRF (and SAE report, if applicable).

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

8.7.7. Recording Poststudy Adverse Events

A poststudy AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.6.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

9. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

9.1. Primary, Secondary and Exploratory Study Endpoints

9.1.1. Primary Endpoint

- ORR, defined as the proportion of patients who achieve a best response of CR or PR per the Lugano Classification (Cheson et al 2014) (Appendix 4) and determined by the investigator

9.1.2. Secondary Endpoints

- Efficacy endpoints assessed by the investigator using the Lugano Classification:
  - Complete response rate, defined as the proportion of patients who achieve a best response of complete response
  - Duration of response, defined as the time from the date that response criteria are first met to the date that disease progression is objectively documented or death, whichever occurs first
  - Time to response, defined as the time from the date of the first dose of tislelizumab to the time the response criteria are first met
- Safety and tolerability of tislelizumab, as defined by:
  - The incidence and severity of AEs according to NCI-CTCAE v5.0
  - Changes in vital signs, physical findings, and clinical laboratory results

9.1.3. Exploratory Endpoints

- Progression-free survival, as assessed by the investigator using the Lugano Classification and defined as the time from the first dose of tislelizumab to the date of disease progression or death, whichever occurs first
- Overall survival, defined as the time from the first dose of tislelizumab to the date of death from any cause
- Patient-reported outcomes, as measured using EQ-5D-5L and EORTC QLQ-C30
- Clinical outcomes (eg, PFS and duration of response) per the LYRIC criteria (Cheson et al 2016) (Appendix 5) and as determined by the investigator, and ancillary exploratory studies by centralized imaging for a subset of patients (to be determined at the time of the primary analysis)
- Status of exploratory biomarkers in the study population, and their association with disease status, response, and/or resistance mechanisms of tislelizumab

- PK of tislelizumab: Summary of serum concentrations of tislelizumab including but not limited to tislelizumab C_{trough}
- Immunogenicity of tislelizumab: assessment of the incidence of ADAs

9.2. Statistical Analysis

9.2.1. Analysis Sets

The Safety Analysis Set includes all patients who receive at least 1 dose of tislelizumab.

This will be the primary analysis set for the efficacy and safety analyses, which will be performed for both cohorts combined.

The PK Analysis Set includes all patients for whom valid tislelizumab PK parameters can be estimated.

9.2.2. Patient Disposition

The number of patients enrolled, treated, and discontinued from study drug will be counted by cohort and overall. The primary reason for study drug discontinuation will be summarized according to the categories in the eCRF. The end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

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

9.2.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by cohort and overall using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cHL diagnosis, number of prior lines of therapy for cHL; categorical variables include gender, ECOG, systemic symptoms (B symptoms), International Prognostic Score (Appendix 3) at diagnosis, bulky disease defined as mediastinal mass ratio of 0.33 or size of any single node/nodal mass is ≥ 10 cm in diameter, and erythrocyte sedimentation rate.

9.2.4. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized by cohort and overall and listed by drug and drug class in the clinical study report for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. A listing of prior and concomitant medications will be included in the clinical study report of this protocol.

9.3. Efficacy Analyses

9.3.1. Primary Efficacy Endpoint Analysis

The primary endpoint is ORR assessed by the investigator per the Lugano Classification (Cheson et al 2014) (Appendix 4). The ORR is defined as the proportion of patients achieving a best response of CR or PR.

Best overall response is defined as the best response recorded from the first dose of tislelizumab until data cut or the start of a new anti-lymphoma therapy. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders. For each cohort, estimate of ORR and its corresponding Clopper-Pearson 95% confidence interval (CI) will be presented. The proportion for each of the response categories will also be summarized.

The primary efficacy analysis for both cohorts combined will be conducted at least 12 weeks after the last patient has been dosed, either having undergone the first response assessment or having withdrawn prior to the first response assessment. A separate end-of-study analysis will be performed, details of which will be provided in the Statistical Analysis Plan (SAP).

In the event that some patients do not have central confirmation of cHL diagnosis, a sensitivity analysis may be performed on the patients in the Safety Analysis Set with central confirmation of cHL diagnosis.

The historical control ORR is assumed to be approximately 45% based on previous clinical trials (Moskowitz et al 2013). The null and alternative hypotheses are set as follows:

H_0: ORR = 0.45 for Cohort 1 and Cohort 2 combined

H_a: ORR > 0.45 for Cohort 1 and Cohort 2 combined

A binomial exact test will be performed to test the hypothesis. If the 1-sided p-value is less than or equal to 0.05 (which is equivalent to observing 25 or more responders out of 42 patients), it will be concluded that single agent tislelizumab statistically significantly increases ORR compared to the historical control. The superiority of single agent tislelizumab will be demonstrated at a 1-sided level alpha of 0.05. A 2-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the rate estimate; a 2-sided 90% CI will also be constructed to be consistent with the 1-sided 95% confidence bound.

9.3.2. Secondary Efficacy Endpoint Analysis

The rate of complete response as determined by the investigator and the corresponding Clopper-Pearson 95% CI will be presented for the cohorts combined. Patients with no post-baseline response assessment (due to any reason) will be considered non−responders.

Duration of response will be analyzed using the Kaplan-Meier method. Patients who receive other anticancer therapies, including HSCT (in Cohort 2), before having an event (disease progression or death, whichever occurs first), will be censored. Time to response will be analyzed using descriptive statistics such as mean, median, and standard deviation. Only patients who have achieved an overall response will be included in the analysis of duration of response and time to response. In addition, sensitivity analyses will be performed using the European Medicines Agency (EMA) censoring rules and censoring only for HSCT.

9.3.3. Exploratory Analyses

The distribution of PFS will be estimated overall using the Kaplan-Meier method. Patients who receive other anticancer therapies, including HSCT (in Cohort 2), before having an event (disease progression or death, whichever occurs first), will be censored. Median and other quartiles of PFS will be estimated with 95% CI using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). In addition, sensitivity analyses will be performed using EMA censoring rules and censoring only for HSCT. PFS rate at selected time points will be estimated with its 95% CI using Greenwood's formula. Details of the censoring rules for PFS will be provided in the SAP.

Overall survival will be censored at the last date known to be alive. Overall survival will be analyzed using the same methods employed on the PFS analysis.

Descriptive analyses (mean, standard deviation, median, range) and mean changes (standard deviation) from baseline for the scores from the EORTC QLQ-C30 scales, and the scores of the visual analog scale (VAS) of the EQ-5D-5L will be computed and summarized for each assessment time point.

Clinical outcomes by tumor assessment will be summarized using the LYRIC criteria (Cheson et al 2016) (Appendix 5).

Efficacy variables (eg, ORR and PFS) will be correlated to biomarker expression level to identify a potential biomarker defining a subset that is more sensitive to the PD-1 treatment.

Correlation between steady-state trough serum concentration of tislelizumab and efficacy or safety endpoints may be explored.

9.4. Safety Analysis

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0. Laboratory values (eg, hematology, clinical chemistry), vital signs, and physical examination assessments will also be used in determining safety. Descriptive statistics will be used to analyze all safety data by cohort and overall.

9.4.1. Extent of Exposure

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

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation due to AEs will be summarized. The cycle in which the first dose interruption occurred will be summarized using descriptive statistics. Frequency of dose interruptions will be summarized by categories.

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

9.4.2. Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA lower level term closest to the verbatim term. The linked MedDRA Preferred Term and primary System Organ Class are also captured in the database.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 90 days following study drug discontinuation, regardless of whether or not the patient starts a new anti-lymphoma therapy. TEAEs also include all irAEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug. For patients who begin new anticancer therapy, only irAEs will be reported during the 90-day period after the last dose of study treatment. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by System Organ Class and Preferred Term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within a System Organ Class and Preferred Term, even if the patient experienced more than 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. Treatment-related AEs include those events considered by the investigator to be definitely, possibly, or probably related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAEs with Grade 3 or above, irAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation or dose interruption will be summarized.

Safety data will be monitored throughout the study. At approximately 9 weeks after the 20th patient has been dosed, data from the first 20 patients in the combined cohorts will be compared against pre-specified safety stopping criteria. The stopping criteria will be applied for deaths from causes other than disease progression (non-PD), treatment-emergent SAEs, and treatment-emergent Grade 3 or higher immune-related AEs. The stopping criteria for the aforementioned types of safety events are summarized in Table 5 and are based on cutoffs representing a greater than 85% Bayesian posterior probability of exceeding a set event rate threshold where each event rate threshold is based approximately in reference to the results of approved anti-PD1 treatments, including nivolumab (Armand et al 2018, Opdivo® US Prescribing Information). For non-PD deaths, the stopping criterion is defined as having a greater than 85% Bayesian posterior probability of exceeding the event rate of 5%. Similarly, for treatment-emergent SAEs and treatment-emergent Grade 3 or higher immune-related AEs, the event rates for comparison are 35% and 20%, respectively. The prior distributions for non-PD deaths, treatment-emergent SAEs and treatment-emergent Grade 3 or higher immune-related AEs are based approximately on the results of the BGB-A317-203 trial (data on file) and are Beta (0.05, 4.95), Beta (0.85, 4.15) and Beta (0.6, 4.4), respectively.

Table 5: Safety Stopping Criteria

Event type	Event rate threshold	Prior distribution	Number of patients with event where posterior probability of event rate exceeding threshold is greater than 85% among 20 subjects
Deaths from causes other than disease progression	5%	Beta (0.05, 4.95)	≥ 3
Treatment-emergent SAEs	35%	Beta (0.85, 4.15)	≥ 11
Treatment-emergent Grade 3 or higher immune-related AEs	20%	Beta (0.6, 4.4)	≥ 7

9.4.3. Laboratory Analyses

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

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

9.4.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse, temperature) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

9.5. Pharmacokinetics Analysis

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

The tislelizumab C_{trough} will be tabulated and summarized for each cycle at which PK is to be measured. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK analyses may be conducted as appropriate.

9.6. Immunogenicity Analysis

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

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

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

9.7. Sample Size Consideration

A total of approximately 42 patients will be enrolled.

The results from a previous clinical trial of tislelizumab (Song et al 2018) yielded an ORR of 85.7% in a predominantly brentuximab vedotin-naive population. Assuming an alternative ORR of 65% compared to the null ORR of 45% in Cohort 1 and Cohort 2 combined, using a binomial exact test, the power to reject the null hypothesis with 42 patients at a 1-sided alpha of 0.05 is greater than 80%.

9.8. Interim Analysis

No interim analysis is planned for this study.

10. STUDY COMMITTEES AND COMMUNICATIONS

10.1. Safety Monitoring Committee

The first safety review will occur after at least 20 patients have been on treatment for at least 9 weeks in order to determine if the proposed dosing schedule of tislelizumab is safe and tolerable. As enrollment will be discontinued at approximately 42 patients dosed, safety monitoring analysis will be conducted at the time of primary analysis.

The Safety Monitoring Committee may recommend study modification including termination of the study due to safety and/or efficacy concerns. The function and membership of the Safety Monitoring Committee will be described in the Safety Monitoring Committee Charter.

In addition to the planned review(s), ad hoc reviews may take place based on new information.

Following Safety Monitoring Committee review and discussion, the sponsor will make all final decisions regarding any change in study conduct. Please see the details in the Safety Monitoring Committee Charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits of the clinical study. BeiGene will provide thirty calendar days' prior written notice of any audit to ensure that all members of the LYSARC Team involved in the study will be present. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, BeiGene and LYSARC 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 Institutional Review Board/Independent Ethics Committee members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records, and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials (if allowed), 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 in order to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will return to sponsor and/or 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 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.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the informed consent forms, any information to be given to the patient, and relevant supporting information must be submitted to the Institutional Review Board/Independent Ethics Committee by the principal investigator/the sponsor, unless local laws and regulations require otherwise, and reviewed and approved by the Institutional Review Board/Independent Ethics Committee before the study is initiated. In addition, any patient recruitment materials must be approved by the Institutional Review Board/Independent Ethics Committee.

The principal investigator/the sponsor is responsible for providing written summaries of the status of the study to the Institutional Review Board/Independent Ethics Committee annually or more frequently in accordance with the requirements, policies, and procedures established by the Institutional Review Board/Independent Ethics Committee. Investigators/the sponsor are/is also responsible for promptly informing the Institutional Review Board/Independent Ethics Committee of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators/the sponsor must comply with requirements for reporting SAEs to the local health authority and Institutional Review Board/Independent Ethics Committee. 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 Institutional Review Board/Independent Ethics Committee and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the Institutional Review Board/Independent Ethics Committee together with, if applicable, a revised model informed consent form in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the Institutional Review Board/Independent Ethics Committee 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 informed consent form confirming their willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample informed consent form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final Institutional Review Board/Independent Ethics Committee-approved informed consent forms must be provided to the sponsor for health authority submission purposes according to local requirements.

The investigator is responsible for obtaining written informed consent from everyone participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The informed consent forms 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 prior to participation in the study.

The informed consent forms 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 Institutional Review Board/Independent Ethics Committee -approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the informed consent forms (or to a significant new information/findings addendum in accordance with applicable laws and Institutional Review Board/Independent Ethics Committee policy) during their participation in the study. For any updated or revised informed consent forms, 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 informed consent forms for continued participation in the study.

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

13.4. Patient and Data Confidentiality

The sponsor will maintain confidentiality and privacy standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed informed consent form (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.

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.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Information on maintaining patient confidentiality in accordance to applicable national and international (such as the EU General Data Protection Regulation) patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the informed consent form or as a separate signed document (for example, in the US, a study-center specific Health Insurance Portability and Accountability Act [HIPAA] consent may be used).

The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of BeiGene 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 BeiGene. 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 includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an electronic data capture system. Data required by the protocol includes the first letter of the first name, the first letter of the last name, and month and year of birth, for patients included in France and Belgium in order to optimize the collection of tumor blocks from anatomopathology laboratories and to facilitate biological samples reconciliation.

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 investigator or designee as identified on the Statement of Investigator Form must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs should not be made available in any form to third parties, except for authorized representatives of the sponsor or appropriate regulatory authorities.

14.1.2. Data Management/Coding

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

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file which 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 (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

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

AEs will be coded using MedDRA. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Data Integrity and In-House Blinding

Due to the open-label design of the study, access to the patient-level clinical data in the electronic data capture system will only be assigned to predefined study personnel. Functions/persons with access to the electronic data capture system shall be prohibited from using the electronic data capture system to generate unnecessary listings/summaries that may introduce unwanted bias or

sharing such outputs from the electronic data capture system with other functions/persons who do not have access to the electronic data capture. Although the trial is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3. 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 the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, Institutional Review Board/Independent Ethics Committee, and governmental approval with correspondence, informed consent, 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 (although not be limited to) 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 log, 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 assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating 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 or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility and 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 the documents, special arrangements must be made between the investigator and the sponsor 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 in storage by the sponsor for a period up to 1 year for purposes of this study.

14.4. Protocol Deviations

The investigator is responsible for ensuring 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, if applicable, to the Institutional Review Board/Independent Ethics Committee, in accordance with established Institutional Review Board/Independent Ethics Committee policies and procedures.

14.5. Publication and Data Sharing Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that 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 BeiGene and LYSARC (co-sponsors), regardless of the outcome of the study. The data generated in this clinical study are confidential. As this is 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 2023).

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. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

14.6. Study and Study Center Closure

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

- Return of all study data to the sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Shipment of all samples to a central laboratory

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance with this protocol, GCP, 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 prior to its taking effect.

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

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

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

14.7. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study, whether patentable or not, are the sole property of BeiGene, and are hereby assigned to BeiGene.

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) will be kept 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 BeiGene.

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 Institutional Review Board/Independent Ethics Committee solely for the evaluation of the study.
- Information that is necessary to disclose to provide appropriate medical care to a patient.
- Study results that may be published.

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

	Screening [1]	Treatment Period			Safety Follow-up [4]	Safety/Survival/Efficacy Follow-up [5]
		Cycle 1 (21 Days) [2]	Cycle 2 and additional cycles (every 21 days)	EOT [3]		
Days	-28 to -1	1	1 ± 7	Within 30 days (+ 7) of last dose	Within 30 days (+ 7) of last dose	Every 90 days (± 14) after Safety Follow-up
Informed consent [6]	x					
Inclusion/exclusion criteria	x					
Demographics /Medical history / Prior medications [7]	x					
Vital signs [8]	x	x	x	x	x	
Height and weight [9]	x	x	x	x		
Physical examination	x	x	x	x	x	x [29]
ECOG performance status	x	x	x	x	x	
12-lead ECG [10]	x					
Pulmonary function test [11]	x					
Review adverse events [12]	x	x	x	x	x	x
Review concomitant medications [13]	x	x	x	x	x	x

	Screening [1]	Treatment Period			Safety Follow-up [4]	Safety/Survival/Efficacy Follow-up [5]
		Cycle 1 (21 Days) [2]	Cycle 2 and additional cycles (every 21 days)	EOT [3]		
CBC with differential [14]	x	x	x [27]	x	x	x [29]
Serum chemistry panel [14]	x	x	x [27]	x	x	
Hepatitis B and C and HIV [15]	x					
ESR		x [27]				
Pregnancy test (if applicable)[16]	x		x	x	x	
Thyroid function test [17]		x [27]	x [27] (after C2D1, repeat every odd-numbered cycle)	x	x	
Liver function tests [18]	x	x	x		x	
Pancreatic enzymes [19]	x					
Tumor tissue [20]	x	x [20]		x [20]		
Optional blood collection [21]	x	x	x	x		
Tumor imaging (note separate schedule for PET-CT and CT with contrast)[22]	x	PET-CT: At Week 12 from C1D1, then every 12 weeks for 96 weeks, and every 24 weeks thereafter, ± 14 days CT w/contrast: Every 24 weeks from C1D1, +/- 14 days		x [23]		x [23]
ECHO or MUGA [24]	x					

	Screening [1]	Treatment Period			Safety Follow-up [4]	Safety/Survival/Efficacy Follow-up [5]
		Cycle 1 (21 Days) [2]	Cycle 2 and additional cycles (every 21 days)	EOT [3]		
Survival status						x
Study drug administration		x	x			
Pharmacokinetics [25]		x	x		x	
Anti-drug antibody [26]		x	x		x	
Patient-reported outcomes [28]		x [28]	x [28]		x [28]	

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, cycle; CBC, complete blood count; cHL, classical Hodgkin lymphoma; CR, complete response; CT, computed tomography; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EOS, end of study; EOT, end-of-treatment; ESR, erythrocyte sedimentation rate; FFPE, formalin fixed paraffin-embedded; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HL, Hodgkin lymphoma; MRI, magnetic resonance imaging; irAE, immune-related adverse event; MUGA, multigated acquisition scan; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; PCR, polymerase chain reaction; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetics; SAE, serious adverse event; TSH, thyroid stimulating hormone; T3, triiodothyronine; T4, thyroxine.

1. All assessments mandated throughout the study must be performed on a calendar schedule. Screening procedures must be performed within 28 days prior to the first dose of treatment, unless noted otherwise. Once all screening assessments have been completed and study eligibility has been confirmed, study treatment must commence within 14 days of confirmation, which is within the 28-day screening window prior to the first dose of study treatment. Screening procedures that have a different visit window are indicated in parentheses.
2. If screening lab assessment for eligibility is completed within 3 days of study drug administration, they do not need to be performed again for C1D1. Rescreening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the screening window (Day -28 to Day -1). For C2D1 and all subsequent cycles, hematology and serum chemistry (including liver function tests) should be performed within 48 hours before study drug administration. For serum chemistry panel, a fasting blood sample is taken when possible, unless it is urgent.
3. When patients go off treatment, they will need to have an EOT Visit within 30 days (+ 7 days) of last dose of tislelizumab. This visit may be considered the Safety Follow-up Visit.
4. The mandatory Safety Follow-up Visit should be conducted within 30 days (+ 7 days) of the last dose of study treatment. In addition, telephone contacts (or clinic visit, if preferred) with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or a new anti-lymphoma therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab. All AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after last dose of study treatment. Patients with an ongoing AE that leads to treatment discontinuation will be followed until either the event

resolves, the investigator assesses the event as stable, or the patient is lost to follow up, whichever comes first. Beyond 90 days, investigators should continue to report any SAEs that are believed to be related to study drug if they become aware of them.

5. Following completion of the Safety follow-up phase, every effort should be made to follow patients for survival and for SAEs as described in Section 7.12 approximately every 90 days (± 14 days) until PD, withdrawal of consent, death, loss to follow-up, or EOS, whichever occurs first.
6. Written consent must be obtained prior to performing any protocol specific procedure except those done as standard of care. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg, within 28 days prior to C1D1). Assign patient number when the study informed consent is signed.
7. Includes history for the primary diagnosis (date of HL diagnosis and last recurrence, HL subtype, stage, International Prognostic Score [IPS], and biopsy details), treatment of HL including prior systemic, radiation and surgical treatment. Date of last prior cancer treatment must be documented. Report complete medication history for 28 days prior to the Screening Visit (Visit 1).
8. Vital signs to include temperature, blood pressure, and pulse.
9. Height is to be measured only on Day 1 of Cycle 1.
10. A single 12-lead ECG will be performed by qualified site personnel after the patient has rested in a semi-recumbent or supine position for at least 5 minutes. Two copies of the ECG tracing should be obtained at the time of the ECG; the first copy will be kept in the patient's medical chart and the second copy will be kept in the study file for retrospective collection by the sponsor if necessary. The Screening ECG may be performed on Day 1 before the first dose. A single 12-lead ECG can also be performed when clinically indicated at the discretion of the investigator during the study.
11. Pulmonary function tests will include spirometry and lung diffusion capacity and must be performed within 4 weeks prior to first dose of tislelizumab. Pulmonary function tests can also be performed when clinically indicated at the discretion of the investigator during the study.
12. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v5.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
13. All concomitant medications within 28 days prior to first study treatment and 90 days after the last dose of study treatment should be recorded in the eCRFs. In addition, telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or a new anti-lymphoma therapy) at 60 and 90 days (± 14 days) after the last dose of tislelizumab. Any new anti-lymphoma therapy, if taken after treatment discontinuation, will also be recorded.
14. CBC and comprehensive serum chemistry panel, if obtained ≤ 3 days prior to Day 1 of Cycle 1 as part of screening, may be used as baseline, in which case retesting on Day 1 of Cycle 1 is not required.
15. Testing will be performed at screening and includes Hepatitis C virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb) and Hepatitis B core antibody (HBcAb). HIV results will be recorded if previously known. Patients who are HBcAb positive or HCV antibody positive at screening must not be enrolled until further testing by PCR to assess Hepatitis B or HCV viral load for determination of study eligibility as per Inclusion/Exclusion Criteria. (See Section 4 and Section 7.6.3 for additional information.)
16. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening no more than 7 days before the first dose of study drug. Urine pregnancy tests will be performed every cycle beginning with Cycle 2 during the treatment phase of the study. Pregnancy tests must be continued every 3 weeks for at least 30 days after the last dose of study drug. Pregnancy tests will be evaluated by local laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
17. TSH, free T4, and free T3 evaluations will be performed during the treatment period, at the EOT Visit and at the Safety Follow-up Visit.
18. Liver function tests include ALT, AST, alkaline phosphatase, total bilirubin, and conjugated bilirubin and will be evaluated by a local laboratory. Liver function tests are required weekly during Cycles 1 and 2, with further monitoring if increases are observed in the first 2 cycles, according to Appendix 6.
19. Pancreatic enzymes (amylase and lipase) will be tested if clinically indicated while on treatment.
20. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 unstained slides) for central confirmation of cHL diagnosis (central confirmation of diagnosis is not required for study entry) and biomarker analysis. Tumor tissue submission is mandatory for all patients who consent to

participate in the study, and an additional fresh baseline tumor biopsy (optional) at screening is strongly recommended. If a biopsy is not performed at screening, a sample of archival tumor tissue should be submitted from the confirmation of any relapse, with the most recent relapse sample being preferred. If tissue from a relapse is unavailable, archival tissue from the initial diagnosis may be submitted. An optional tumor biopsy will be taken from accessible tumor sites at the time of partial response to explore tumor biomarkers of tislelizumab response and resistance. For patients who have a confirmed disease progression during the study, optional biopsies will also be taken to explore resistance mechanisms (written informed consent is required prior to fresh tumor biopsy). If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the screening biopsy.

21. Optional blood samples will be taken at screening, at Weeks 3, 6, 12, 24, 48, and at the time of PD or 6 months after treatment to explore the association of blood-based biomarkers with response, resistance and prognosis to tislelizumab.
22. Tumor imaging (PET-CT and CT with contrast of neck, chest, abdomen and pelvis) will be performed within 28 days prior to the first dose of study drug treatment. Any qualified imaging assessments already completed during the regular work-up of the patient are accepted within 28 days prior to start of treatment, including before signing the informed consent form, and can be considered as the screening/baseline image for this study. Imaging timing should follow calendar days and should not be adjusted for treatment delays. Tumor assessments by CT with contrast should be performed at screening and every 24 weeks (± 14 days) starting from Cycle 1 Day 1, until PD or treatment discontinuation, whichever is earlier. Target and non-target lesions must be identified at the time of screening and the same lesion(s) must be re-assessed by the investigator at each time point in a consistent manner in accordance with the Lugano Classification (Cheson et al 2014). The same diagnostic modality must be used throughout the study. At time points in which a CT scan with contrast is required, PET-CT may be adequate if the CT portion of the PET-CT is of diagnostic quality and contrast is administered. Total body MRI or CT without contrast of the chest plus MRI of the neck, abdomen, and pelvis may be substituted for CT if CT with contrast is contraindicated. PET-CT should be performed, in addition to during screening, at Week 12 from C1D1, then every 12 weeks for 96 weeks, and every 24 weeks thereafter (± 14 days). PET-CT should also be performed for PD suspected clinically and CR suspected clinically or by CT.
23. Tumor imaging for the EOT Visit does not have to be performed if the most recent tumor imaging was performed within the previous 6 weeks. For patients who discontinue study treatment for reason other than PD, tumor imaging will be performed every 90 days (± 7 days) until PD, withdrawal of consent, death, loss to follow-up, or EOS, whichever occurs first.
24. ECHO or MUGA is required at screening unless performed within 90 days of enrollment, subject to review and agreement by the medical monitor or designee.
25. Samples for PK analysis will be collected only at sites that are able to adequately follow the sampling, handling, and processing procedures described in the Laboratory Manual. Samples for PK analysis will be collected predose (within 60 minutes before start of infusion) on Day 1 of Cycles 1, 2, 5, 9, and 17 and postdose (within 30 minutes after the end of infusion) on Day 1 of Cycles 1 and 5. Additional PK samples will be collected at the Safety Follow-up Visit. Should a patient experience any ≥ Grade 3 irAE, additional blood PK samples may be taken to determine the serum concentration of tislelizumab.
26. Samples for anti-tislelizumab antibody analysis will be collected only at sites that are able to adequately follow the sampling, handling, and processing procedures. Procedures for collection of these samples are described in the Laboratory Manual. Blood for anti-tislelizumab antibodies should be collected within 60 minutes before start of infusion on Day 1 of Cycles 1, 2, 5, 9, and 17, and at the mandatory Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for PK predose sampling. In patients who discontinue study treatment before 6 months, every effort should be made to analyze anti-tislelizumab antibodies approximately 6 months after the first dose. Analysis will be performed by a central laboratory.
27. These tests should be completed within 3 days before the start of next cycle.
28. All patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug on C1D1, then every 12 weeks for 96 weeks, then every 24 weeks thereafter until PD or treatment discontinuation, whichever is earlier, and at the Safety Follow-up Visit.
29. Physical examination and CBC will be performed only for Efficacy Follow-up.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	**CBC With Differential**
Sodium	Hematocrit
Potassium	Hemoglobin
Chloride	Platelet
Bicarbonate	WBC with differential:
BUN	Neutrophil
Creatinine	Lymphocyte
LDH	Monocyte
Glucose	Eosinophil
Calcium	Basophil
AST (SGOT)	
ALT (SGPT)	
Total bilirubin	
Conjugated bilirubin	
Alkaline phosphatase	
Total protein	
Magnesium	
Phosphorus	
Uric acid	
Albumin	
Creatine kinase (CK)	
Creatine kinase-cardiac muscle isoenzyme (CK-MB)*	

* In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; CBC, complete blood count; LDH: lactate dehydrogenase; SGOT: glutamic-oxaloacetic transaminase; SGPT: glutamic-pyruvic transaminase; WBC: white blood cell (count).

APPENDIX 3. INTERNATIONAL PROGNOSTIC SCORE

- Male sex
- Age ≥ 45 years
- Stage IV
- Hemoglobin < 10.5 g/dL
- White blood count ≥ 15 x 10^9/L
- Lymphocyte count < 0.6 x 10^9/L or < 8% of differential
- Albumin < 4 g/dL

APPENDIX 4. THE LUGANO CLASSIFICATION

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response Score 1, 2, 3* with or without a residual mass on 5PS□	Complete radiologic response (all of the following):
Lymph nodes and extra-lymphatic sites	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 LDi • 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, IHC negative

Response and Site	PET-CT-Based Response	CT-Based Response
Partial Lymph nodes and extra-lymphatic sites	Partial metabolic response 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	Partial remission (all of the following): • ≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites • When a lesion is too small to measure on CT, assign 5 mm x 5 mm as the default value • When no longer visible, 0 x 0 mm • For a node > 5 mm x 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	CT-Based Response
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 SPD 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 1 of the following:

Response and Site	PET-CT-Based Response	CT-Based Response
Individual target nodes/nodal masses Extranodal 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	PPD progression: An individual node/lesion must be abnormal with: • LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi 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 at least 2 cm from baseline • New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
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

As published by Cheson et al 2014.

Abbreviations: CT: Computed tomography; FDG: fluorodeoxyglucose; GI: gastrointestinal; IHC: immunohistochemistry; LDi: longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET: positron emission tomography; PET-CT: positron emission tomography-computed tomography; PPD: product of the LDi and perpendicular diameter; SDi: shortest axis perpendicular to LDi; SPD: sum of the product of the perpendicular diameters for multiple lesions

* Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extra-nodal lesions selected to be clearly measurable in two 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 (GI) 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, GI 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).
** Splenomegaly defined as vertical spleen length > 13 cm.
▫ 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

APPENDIX 5. COMPARISON OF LYRIC CRITERIA AND LUGANO CLASSIFICATION

Criteria	CR	PR	PD**
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions: Indeterminate Response (IR) - IR1: ≥ 50% increase in SPD* in first 12 weeks IR2: < 50% increase in SPD with: New lesion(s), OR ≥ 50% increase in PPD of a lesion or set of lesions at any time during treatment IR3: Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

As published by Cheson et al 2016.
Abbreviations: CR: complete response; FDG: fluorodeoxyglucose; IR: indeterminate response; LDi, longest transverse diameter of a lesion; LYRIC, Lymphoma Response to Immunomodulatory Therapy Criteria; PD: disease progression; PPD: product of the LDi and perpendicular diameter; PR: partial response.

Note: The study will use a modified version of the LYRIC criteria and Lugano Classification. For instances of observed indeterminate response (IR1, IR2, or IR3) as assessed by the investigator, pseudo-progression will be documented in the case report form to collectively represent all of the scenarios of indeterminate response.

* SPD: sum of the product of the diameters
** In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated and the patient should be considered to have true disease progression if the SPD of the target lesion has increased further. Finally, if a patient is assessed as having IR (or pseudo-progression) and then true PD at a subsequent time point, the initial IR (or pseudo-progression) assessment should be corrected to PD.

APPENDIX 6. IMMUNE-RELATED ADVERSE EVENTS EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE 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 irAEs 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 irAE diagnosis:

- What was the temporal relationship between the initiation of tislelizumab and the adverse event?
- 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 irAE field, associated with the AE in the eCRF should be checked.

Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

Immune-Related Toxicity	**Diagnostic Evaluation Guideline**
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. 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.

Immune-Related Toxicity	Diagnostic Evaluation Guideline
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, 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 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including: Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy).
Renal toxicity	Review hydration status, and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.
Primary adrenal insufficiency	Evaluate ACTH (AM), cortisol level (AM), basic metabolic panel (sodium, potassium, carbon dioxide, glucose). Consider ACTH stimulation test for indeterminate results. If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically:

Immune-Related Toxicity	Diagnostic Evaluation Guideline
	Evaluate for precipitating cause of crisis such as infection Perform an adrenal CT for metastasis/hemorrhage
Hematologic toxicity	May refer to ASCO guidelines (Brahmer et al 2018) for the diagnostic work-up of the following toxicities. Evaluation by a hematologist (may be treating physician, if appropriate) is strongly recommended. • Autoimmune hemolytic anemia • Acquired TTP • Hemolytic uremic syndrome • Aplastic anemia • Immune thrombocytopenia • Acquired hemophilia

Abbreviations: ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; AM, morning; ANA, antinuclear antibody; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase - cardiac muscle isozyme; 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; TTP, thrombotic thrombocytopenia purpura; UEC, urea, electrolytes, and creatinine.

Treatment of Immune-Related Adverse Events

- Immune-related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related 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 irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF] or azathioprine)
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy
- Patients who require prolonged corticosteroid treatment of >12 weeks for a drug-related AE must permanently discontinue from study therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with 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 0-1.
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 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider pneumocystis infection prophylaxis. Taper corticosteroids over 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 on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment, or in the event of recurrent pneumonitis.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for pneumocystis infection and other adverse steroid effects (eg, blood glucose monitoring, vitamin D/calcium supplement).	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms		Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72 - 96 hours.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Guillain-Barré syndrome	Treat with intravenous immunoglobulin 0.4 g/kg/day for 5 days or plasmapheresis. Consider corticosteroids (methylprednisolone 2 to 4 mg/kg/day) followed by slow taper. Monitor for concurrent autonomic nervous system 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.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects (eg, blood glucose monitoring, vitamin D/calcium supplement). If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Treat with topical emollients and/or mild to moderate potency topical corticosteroids. Counsel patients to avoid skin irritants and sun exposure.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Rash covers 10%-30% of BSA	Consider initiating prednisone (or equivalent) at 1 mg/kg, tapering for a period of ≥ 4 weeks. In addition, treat with topical emollients, oral antihistamines, and medium to high potency topical corticosteroids.	Consider holding tislelizumab and monitor weekly for improvement. If not resolved, interrupt treatment until dermatitis has improved to Grade 1.
	3 Rash covers > 30% BSA or grade 2 with substantial symptoms	Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. Initiate (methyl)prednisolone (or equivalent) 1 to 2 mg/kg, tapering for a period of ≥ 4 weeks.	Hold study treatment and consult with a dermatologist as needed.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Hospitalize the patient and treat in collaboration with dermatology. Treat with intravenous (methyl)prednisolone 1 to 2 mg/kg (or equivalent) with tapering for a period of ≥ 4 weeks once toxicity resolves.	Permanently discontinue study treatment and hospitalize the patient.
	Stevens-Johnson syndrome or toxic epidermal necrolysis	Refer the patient for specialized assessment and treatment.	Hold study treatment if signs and symptoms of Stevens-Johnson syndrome or toxic epidermal necrolysis. If Stevens-Johnson syndrome or toxic epidermal necrolysis of any grade is confirmed, permanently discontinue tislelizumab.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Withhold study treatment until the event has resolved or improved to baseline grade and prednisolone has been tapered to ≤ 10 mg/day. Tislelizumab may be reintroduced only: 1) after the patient's signs and symptoms of hepatitis return to baseline, and 2) if after careful consideration, the expected benefit of a rechallenge outweighs the risk to the patient.
	3 ALT or AST 5-20X ULN	Immediately start methylprednisolone 1 to 2 mg/kg (or equivalent). Monitor closely. If no improvement after 3 days, consider additional treatment options (mycophenolate mofetil or azathioprine). ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 to 2 mg/kg (or equivalent) and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Permanently discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 ALT or AST > 20X ULN	Immediately begin treatment with methylprednisolone 2 mg/kg (or equivalent). Monitor closely. Obtain hepatology consultation. Consider additional treatment options (mycophenolate mofetil or azathioprine).	Permanently discontinue study treatment.
	Hy's Law: ALT or AST > 3X ULN and total bilirubin > 2X ULN; absence of initial findings of cholestasis or other reason(s) for concurrent increased AST or ALT, and total bilirubin	Hepatology consultation Manage per hepatology consultation and per institutional guidance	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone (Grade 2) change to pulsed IV methylprednisolone • If on IV add mycophenolate mofetil (MMF) 500-1000 mg twice a day or azathioprine (Grade 3 and 4) • Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Creatinine > 6X 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 or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9–27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks	Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes	Continue study treatment
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1
	3 and 4 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline	Continue study treatment
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection	Discontinue study treatment
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment
	2 Moderate weakness with/without pain	If CK is 3X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.
Myocarditis	**1** 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; 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, 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 baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	Follow the same study drug management for Grade 1
	3 Severe symptoms with mild exertion		Discontinue study treatment
	4 Life-threatening		Discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Primary adrenal insufficiency	**1** Asymptomatic or mild symptoms	Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. Titrate dose up or down as symptoms dictate.	Consider holding study treatment until patient is stabilized on replacement hormone
	2 Moderate symptoms, able to perform ADL	Endocrine consultation Initiate outpatient treatment at 2-3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days Maintenance therapy as in Grade 1.	Consider holding study treatment until patient is stabilized on replacement hormone
	3-4 Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and stimulation testing will be needed]) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in Grade 1	Hold study treatment until patient is stabilized on replacement hormone

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hematologic		In general, refer to the ASCO practice guidelines on diagnostic work-up and management of these immune-related hematologic toxicities (Brahmer et al 2018). Treatment algorithms may vary according to individual institutional guidelines. In all cases of confirmed diagnosis, report to principal investigator of institution and Sponsors' coordinating investigator(s) and medical monitor(s).	
Autoimmune hemolytic anemia (AHA)	**1** Hgb < LLN to 10.0 g/dL; < LLN to 6.2 mmol/L; < LLN to 100 g/L	Close clinical follow-up and laboratory evaluation	Continue study treatment
	2 Hgb < 10.0 to 8.0 g/dL; < 6.2 to 4.9 mmol/L; < 100 to 80 g/L due to AHA	Administer 0.5-1 mg/kg/d prednisone equivalents or as directed by treating hematologist and/or the principal investigator	Hold study treatment and consider permanent discontinuation
	3 Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated due to AHA	Hematology evaluation and hospital admission if indicated Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	Permanently discontinue study treatment
	4 Life-threatening consequences; urgent intervention indicated	Hematology evaluation and hospital admission Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	Permanently discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hemolytic uremic syndrome	**1-2** Evidence of RBC destruction without clinical consequences or anemia, thrombocytopenia Grade 2	Close clinical follow-up and laboratory evaluation Supportive care	Continue study treatment
	3 Laboratory findings with clinical consequences	Hematology evaluation and hospital admission if indicated Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	Permanently discontinue study treatment
	4 Life-threatening consequences		
Acquired hemophilia	**1** Mild, 5-40% of normal factor activity in blood, 0.05-0.4 IU/mL of whole blood	Administer 0.5-1 mg/kg/d prednisone or as directed by treating hematologist and/or the principal investigator Transfusion support as required Treatment of bleeding disorders	Hold study treatment and discuss resumption with patient only after taking into account the risks and benefits
	2 Moderate, 1-5% of normal factor activity in blood, 0.01-0.05 IU/mL of whole blood	Hematology evaluation Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	
	3-4 Severe, < 1% of normal factor activity in blood, < 0.01 IU/mL of whole blood	Hematology evaluation and hospital admission Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	Permanently discontinue study treatment
Acquired TTP	**1** Evidence of RBC destruction without anemia, renal insufficiency, or thrombocytopenia clinically	Stabilize patient (if needed) with any critical organ dysfunction stabilized Hematology evaluation Administer treatment based on recommendation from the treating hematologist and/or the principal	Hold study treatment and discuss resumption only after taking account the risks/benefits, noting that there are currently no data to recommend restarting ICPi therapy
	2 Evidence of RBC destruction without		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	clinical consequence with Grade 2 anemia and thrombocytopenia	investigator; consult ASCO guidelines For Grade 4, in conjunction with hematology, initiate plasma exchange according to existing guidelines	
	3 Laboratory findings with clinical consequences (Grade 3 thrombocytopenia, anemia, renal insufficiency > Grade 2)		
	4 Life-threatening consequences (eg, CNS hemorrhage or thrombosis/ embolism or renal failure)		
Aplastic anemia	**1** Nonsevere, > 0.5 polymorphonuclear cells x 10^9/L hypocellular marrow, with cellularity < 25%, peripheral platelet count > 20,000, reticulocyte count > 20,000	Provide growth factor support and close clinical follow-up, and laboratory evaluation Supportive transfusions per existing guidelines	Hold study treatment
	2 Severe, hypocellular marrow < 25% and two of the following: ANC < 500, peripheral platelet < 20,000, and reticulocyte < 20,000	Hematology evaluation Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	
	3-4 Very severe, ANC < 200, platelet count < 20,000, reticulocyte count < 20,000, plus hypocellular marrow < 25%	Hematology evaluation Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines Monitor for weekly improvement	Hold study treatment; if not improved to Grade 1, discontinue study treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Immune thrombocytopenia	**1** Platelet count < 100/μL	Close clinical follow-up and laboratory evaluation	Continue study treatment
	2 Platelet count < 75/μL	Administer prednisone 1mg/kg/d (range, 0.5-2 mg/kg/d) orally for 2-4 weeks before tapering over 4-6 weeks to lowest effective dose (or as directed by treating hematologist and/or the principal investigator); IVIG may be added if more rapid platelet increase is required	Hold study treatment; may resume when Grade 1 or baseline
	3 Platelet count < 50/μL	Hematology evaluation Administer treatment based on recommendation from the treating hematologist and/or the principal investigator; consult ASCO guidelines	
	4 Platelet count < 25/μL		

Abbreviations: ADL, activities of daily living; AE, adverse event; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; BSA, body surface area; CHF, chronic heart failure; CK, creatine kinase; CK-MB, creatine kinase-cardiac muscle isoenzyme; ICPi, immune checkpoint inhibitor; INR, international normalized ratio; IV, intravenous; IVIG, intravenous immunoglobulin; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TTP, thrombotic thrombocytopenia purpura; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light 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

As published by (Oken et al 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 8. 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 sponsor medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

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

APPENDIX 9. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner is considered highly effective form of birth control only under the following preconditions:
  - Vasectomized partner is the sole sexual partner of the WOCBP trial participant
  - Vasectomized partner has received medical assessment of surgical success.
  - NOTE: Sterile males are those for whom azoospermia, in a semen sample examination, has been demonstrated as definitive evidence of infertility.
  - Males with 'low sperm counts' (consistent with 'sub-fertility') are not to be considered sterile for purposes of this study.
- 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, postovulation methods), declaration of abstinence for the duration of exposure to study drug, 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 a highly effective form of birth control, listed above.

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
- ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
- < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

Adapted from Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

APPENDIX 10. EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

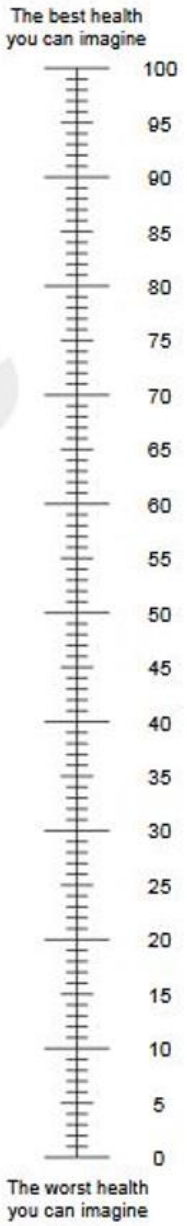
ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



APPENDIX 11. EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

[redacted]

Approved Date 8/23/2023

[redacted]