BeiGene

BGB-A317-203 (NCT03209973)

A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma

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CLINICAL STUDY PROTOCOL

Protocol Title:	**A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma**
Protocol Number:	**BGB-A317-203**
Date of Protocol:	**15-July-2019**
Version:	**6.0**
Study Phase:	**2**
Sponsor:	**BeiGene (Shanghai) Co., Ltd.** **4th Floor, Building D,** **780 Cailun Road,** **China (Shanghai) Pilot-free Trade Zone** **Shanghai, China 201203**
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SIGNATURES

PROTOCOL TITLE: A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma

PROTOCOL NO: BGB-A317-203

DATE OF PROTOCOL: 15-July-2019

PPD

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PROTOCOL AMENDMENT (VERSION 6.0)

The primary reasons for protocol revisions include add CCI and roll-over study. In addition, throughout are administrative updates, editorial changes, and/or style and formatting revisions made with the purpose of improving clarity and consistency throughout the document and with other BeiGene protocols.

Applicable sections	Description of revision
Reason: Text revised as correction and for consistency with other BeiGene protocols	
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS Synopsis: Statistical Methods Section 10.2 Populations Section 10.3 Sample Size Consideration	Change "Population" to "Analysis Set" when it refers to a statistical analysis, changes included: • Change "Populations" to "Analysis Sets" • Change "Safety Population" to "Safety Analysis Set" • Change "Per-protocol Population (PP)" to "Per-protocol (PP) Analysis Set" • CCI
Reason: Corrected heading to keep consistent with that in synopsis	
Section 10.2.5.3: CCI	Previous protocol: CCI After revision: CCI
Reason: CCI	
	CCI

	CCI CCI CCI CCI
Reason: Added roll-over study for continuous treatment and monitoring.	
Section 6.11 End of Study Appendix 5. Schedule of Assessment	**Section 6.11 End of Study** Added below paragraph: Patients still receiving study treatment when the roll-over study is open will transfer to the roll-over study for continuous treatment and monitoring. Patients already off study treatment but not withdrew the ICF will have efficacy (if discontinued not due to disease progression) , safety and survival follow-up (as defined in this parent study) in the roll-over study (see Appendix 5). **Appendix 5. Schedule of Assessment** Added below sentence in footnote:

	26. Subjects still receiving study treatment when the roll-over study is open will transfer to roll-over study for continuous treatment.
Reason: Added sentences to keep consistent with Section 5.1 and Section 5.2.	
Synopsis: Inclusion Criteria Synopsis: Exclusion Criteria	**Synopsis: Inclusion Criteria** Subjects may be enrolled on study only if they meet all the following criteria: **Synopsis: Exclusion Criteria** Subjects will not be enrolled on study if they meet any of the following criteria:
Reason: For completeness, added abbreviations to Table 5, Appendix 6 and Appendix 7.	
Table 5 Immune-related Adverse Events Appendix 6 The Lugano Classification Appendix 7 CCI [redacted]	Added the full list of abbreviations to tables. **Table 5 Immune-related Adverse Events** Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase. **Appendix 6 The Lugano Classification** Abbreviations: PET, Positron Emission Tomography; IHC, Immunohistochemistry; PS, point scale; PPD, purified protein derivative; LD, longest diameter; SD, shortest diameter; CT, Computed Tomography; FDG, fluorodeoxyglucose. CCI [redacted]
Reason: Corrected description for the assessment of height in Section 7.4.2.	
Section 7.4.2 Physical Examination, Vital Signs, Height, and Weight	Delete "height" from the below sentence because height only measured on Day 1 Cycle 1. Previous protocol: A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate), weight and height will be performed at each study visit. After revision: A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate) and weight will be performed at each study visit.

Reason: Remove "following reference documents" because there is only one reference.	
Section 9.1.13 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committees	Previous protocol: To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents: • Tislelizumab Investigator's Brochure. After revision: To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the Tislelizumab Investigator's Brochure.

SYNOPSIS

Name of Sponsor/Company:	BeiGene (Shanghai) Co., Ltd.
Name of Finished Product:	Tislelizumab (BGB-A317)
Name of Active Ingredient:	Tislelizumab, A Novel Anti-PD-1 Monoclonal Antibody
Title of Study:	A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma
Protocol No:	BGB-A317-203
Study Centers:	Approximately 15 sites in China
Study duration: Screening window (up to 28 days); study treatment continues until disease progression, unacceptable toxicity, or study withdrawal for other reason; end of study safety follow-up (30 days); survival follow-up until study termination	**Phase:** 2

Objectives:

Primary:

To evaluate the efficacy of tislelizumab (also known as BGB-A317), assessed by Independent Review Committee (IRC), in subjects with centrally confirmed relapsed or refractory classical Hodgkin lymphoma (cHL), as measured by Overall Response Rate (ORR) per the Lugano Classification (Cheson et al, 2014) (Appendix 6).

Secondary:

To evaluate tislelizumab with respect to:

- Progression-free Survival (PFS) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Duration of Response (DOR) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Rate of complete response (CR) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Time to Response (TTR) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Safety and tolerability

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Methodology: This is an open-label, single-arm, multi-center and multi-national Phase 2 study.	
Planned number of subjects:	Approximately 68 with confirmed cHL
Study Population	**Inclusion Criteria:** Subjects may be enrolled on study only if they meet all the following criteria: 1. ≥ 18 years of age at time of informed consent. 2. Histologically confirmed relapsed or refractory cHL (biopsy from diagnosis or at any relapse is acceptable). 3. Subject must have relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR/complete metabolic response [CMR] or partial response [PR] to most recent therapy) cHL and meets either one of the following criteria: a. Has failed to achieve a response or progressed after autologous hematopoietic stem cell transplant (auto-SCT). b. Has received at least two prior systemic chemotherapy regimens for cHL and is not an auto-SCT candidate due to: chemo-resistant disease (unable to achieve CR or partial response [PR] to salvage chemotherapy), advanced age (≥ 65 years of age), failure to collect stem cells or unable to perform stem cell collection as assessed by the Investigator, or any significant co-existing medical conditions. 4. Subject must have measurable disease defined as ≥ 1 nodal lesion that is > 1.5 cm in the longest diameter, or ≥ 1 extra-nodal lesion (e.g. hepatic nodules) that is > 1 cm in the longest diameter. 5. Availability of archival or fresh tumor tissue sample from an evaluable core or excisional biopsy (10-15 unstained formalin-fixed paraffin embedded [FFPE] slides). Otherwise, subjects may be permitted to enroll on a case-by-case basis after discussion with the Sponsor's medical monitors, provided cHL diagnosis can be confirmed by a central laboratory. 6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 7. Life expectancy ≥ 12 weeks. 8. Subject must have adequate organ functions as indicated by the following laboratory values: a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, independent of growth factor support within 7 days of first dose. b. Platelet ≥ 75 x 10^9/L, independent of growth factor

	support or transfusion within 7 days of first dose. c. Hemoglobin (Hgb) ≥ 8 g/dL or ≥ 5 mmol/L. d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN). e. Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) and alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤ 2.5 x upper limit of normal (ULN), or ≤ 5 x ULN if liver metastases are present. f. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin level < 4 x ULN for subjects with Gilbert's syndrome). 9. International normalized ratio (INR) ≤ 1.5 x ULN and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless patient is receiving anticoagulant therapy and coagulation parameters (prothrombin time [PT/INR] and aPTT) are within intended therapeutic range of intended use of the anticoagulant at time of Screening. Patients with factor inhibitors prolonging PT or INR may be included after discussion with the medical monitor. 10. Subject must have no evidence of dyspnea at rest and a pulse oximetry of > 92% while breathing room air. 11. Subject must have forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) > 60% by pulmonary function test (PFT); carbon monoxide diffusion capacity (DLCO), FEV1 and FVC all > 50 % predicted value; all PFTs must be obtained within 4 weeks prior to the first dose of tislelizumab. 12. Female subject is eligible to enter and participate in the study if she is of: a. Non-childbearing potential (i.e. physiologically incapable of becoming pregnant) including any female who: i. Has had a hysterectomy. ii. Has had a bilateral oophorectomy (ovariectomy). iii. Has had a bilateral tubal ligation. iv. Is post-menopausal (total cessation of menses for ≥ 1 year). b. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test within 7 days of the first dose of study drug. Adequate contraception, when used consistently and in

	accordance with both the product label and instructions of the physician, are defined as: i. Vasectomized partner who is sterile prior to the female subject's study entry and is the sole sexual partner for that female. ii. Any intrauterine device with a documented failure rate of < 1% per year. iii. Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm. 13. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of tislelizumab. 14. Prior chemotherapy, radiotherapy, immunotherapy or investigational therapy (including Chinese herbal medicine and Chinese patent medicine) used to control cancer including locoregional treatment must have been completed ≥ 4 weeks before the first dose of tislelizumab, and all treatment-related adverse events are stable and have either returned to baseline or Grade 0/1 (except for alopecia and hemoglobin). For hemoglobin, please follow inclusion criteria #8c [hemoglobin]). 15. Subject has voluntarily agreed to participate by giving written informed consent. **Exclusion Criteria:** Subjects will not be enrolled on study if they meet any of the following criteria: 1. Nodular lymphocyte-predominant Hodgkin lymphoma or gray zone lymphoma. 2. Prior allogeneic hematopoietic stem cell transplant. 3. History of severe hypersensitivity reaction to monoclonal antibodies. 4. 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. 5. 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 or breast. 6. Prior therapy targeting PD-1 or PD-L1.

	7. Subject with active autoimmune disease or history of autoimmune disease with high risk of recurrence including but not limited to history of immune-related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barrè syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue disease, scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome. Note: Subject is permitted to enroll if he/she has vitiligo, eczema, type I diabetes mellitus, endocrine deficiencies including thyroiditis managed with replacement hormone and/or physiologic corticosteroid. Subject with rheumatoid arthritis and/or other arthropathies, Sjögren's syndrome or psoriasis controlled with topical medication, and subject with positive serology such as positive antinuclear antibody (ANA) or anti-thyroid antibody should be evaluated for presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. 8. Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily Prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of tislelizumab. Note: Adrenal replacement doses of ≤ 10 mg daily Prednisone are permitted in the absence of active autoimmune disease. Topical, ocular, intra-articular, intra-nasal and inhalational corticosteroid (with minimal systemic absorption), a brief course of corticosteroid for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) are allowed. 9. Has history of interstitial lung disease or non-infectious pneumonitis or has evidence of interstitial lung disease or non-infectious pneumonitis currently. 10. QTcF interval > 480 msec, unless secondary to bundle branch block. 11. Serious acute or chronic infection requiring systemic therapy. 12. Known central nervous system (CNS) lymphoma. 13. Underlying medical conditions that, in the Investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events.

14. Known human immunodeficiency virus (HIV), or active hepatitis B (HBV) or hepatitis C (HCV) infection (detected positive by polymerase chain reaction [PCR])

<table>
<tr><td></td><td colspan="2">Inclusion</td><td colspan="2">Exclusion</td></tr>
<tr><td>HIV</td><td colspan="2">Antibody (-)</td><td colspan="2">Antibody (+)</td></tr>
<tr><td rowspan="2">HBV</td><td colspan="2">HBsAg (-) and HBcAb (-)</td><td colspan="2">HBsAg (+)</td></tr>
<tr><td>HBsAg (-) AND HBcAb (+)</td><td>HBV DNA < 1000 IU/ml. After enrollment, monthly monitoring for HBV DNA or anti-viral therapy should be given to prevent HBV reactivation</td><td>HBsAg (-) AND HBcAb (+)</td><td>HBV DNA ≥ 1000 IU/ml</td></tr>
<tr><td rowspan="2">HCV</td><td colspan="2">HCV Ab (-)</td><td rowspan="2">HCV Ab (+)</td><td rowspan="2">HCV RNA ≥ 1 (log_{10}IU/ml)</td></tr>
<tr><td>HCV Ab (+)</td><td>HCV RNA<1 (log_{10}IU/ml)</td></tr>
</table>

HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HIV: human immunodeficiency virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

15. Autologous hematopoietic stem cell transplant within 100 days of first dose of tislelizumab.
16. Use of any live vaccine against infectious diseases (e.g. 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.
17. Major surgery within 4 weeks of the first dose of tislelizumab.
18. Pregnant or lactating women.

Test product, dose and mode of administration:	Tislelizumab 200 mg intravenously (IV) every 3 weeks (Q3W)

Criteria for Evaluation:

Response will be assessed by computed tomography (CT) scan per the Lugano Classification (Cheson et al, 2014) (Appendix 6). Computed tomography scan with contrast will occur at Screening, Week 12, Week 18, then every 12 weeks in the first year, and every 15 weeks thereafter, until progressive disease (PD), new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or end of study (EOS), whichever occurs first. Total body magnetic resonance imaging (MRI) is allowed if CT with contrast is contraindicated. Positron emission tomography (PET)/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered.

Tumor assessment by PET/CT will also be performed at Screening, Week 12, Week 24, Week 42, Week 57, and every 30 weeks thereafter. PET/CT should also be performed at PD suspected clinically or by CT, and CR suspected clinically or by CT.

During treatment with immune checkpoint inhibitor such as with tislelizumab, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Subjects are allowed to continue study treatment if there is suspicion of pseudo-progression, provided they are asymptomatic and have radiographic progression only, until a second consecutive CT scan demonstrates PD at which time

study treatment will be discontinued permanently. Patients should continue on treatment to progression regardless of response status (e.g. in CR).

Subjects will be evaluated for adverse events (AEs) (all grades per National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI-CTCAE v. 4.03]), serious AEs (SAEs), and any AEs requiring study drug interruption or discontinuation, starting from initial dose of study drug until 30 days after last dose of study drug. Subjects who, at the time of PD, have 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 subject is lost to follow-up. If a subject discontinues study treatment due to reason other than PD, then disease status assessment will be captured until start of new anti-cancer therapy, PD, death, lost to follow-up or subject withdraws consent to efficacy follow-up.

Endpoints:

Primary Endpoint:

- ORR is defined as the proportion of subjects who achieves a best response of CR or PR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).

Secondary Endpoints:

- PFS is defined as the time from the first dose of tislelizumab to the date of PD or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- DOR is defined as the time from the date that response criteria are first met to the date of PD or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- Rate of CR is defined as the proportion of subjects who achieves a best response of CR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- TTR is defined as the time from the date of the first dose of tislelizumab to the time the response criteria are first met, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- To evaluate the safety and tolerability of tislelizumab, as defined by:
    - The incidence and severity of adverse events according to NCI-CTCAE v4.03
    - Changes in vital signs, physical findings, and clinical laboratory results

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Statistical Methods:

Analysis sets

The Safety Analysis Set includes all subjects who received any dose of tislelizumab. This will be the population for the safety analyses.

The modified Safety Analysis Set includes all subjects in the Safety Analysis Set who had confirmed cHL. This will be the population for the efficacy analyses.

The Per-protocol (PP) Analysis Set includes subjects who received any dose of tislelizumab and had no major protocol deviations. Criteria for exclusion from the PP Analysis Set will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analysis.

CCI [redacted].

Primary Efficacy Analysis

In relapsed or refractory Hodgkin lymphoma (HL), ORR with single agent treatment as historical control is assumed to be approximately 35% based on historical trials. The ORR of tislelizumab in this study is assumed as 55%, which is deemed a clinically meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR = 35%

H_a: ORR > 35%

A binomial exact test will be performed for hypothesis testing in the modified Safety Analysis Set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the single agent tislelizumab statistically significantly increases ORR compared with historical controls. Therefore, the superiority of single agent tislelizumab will be demonstrated.

A two-sided Clopper-Pearson 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate.

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

The primary efficacy analysis will be conducted approximately 8 months after the first dose of the last subject, and will be based on the modified Safety Analysis Set.

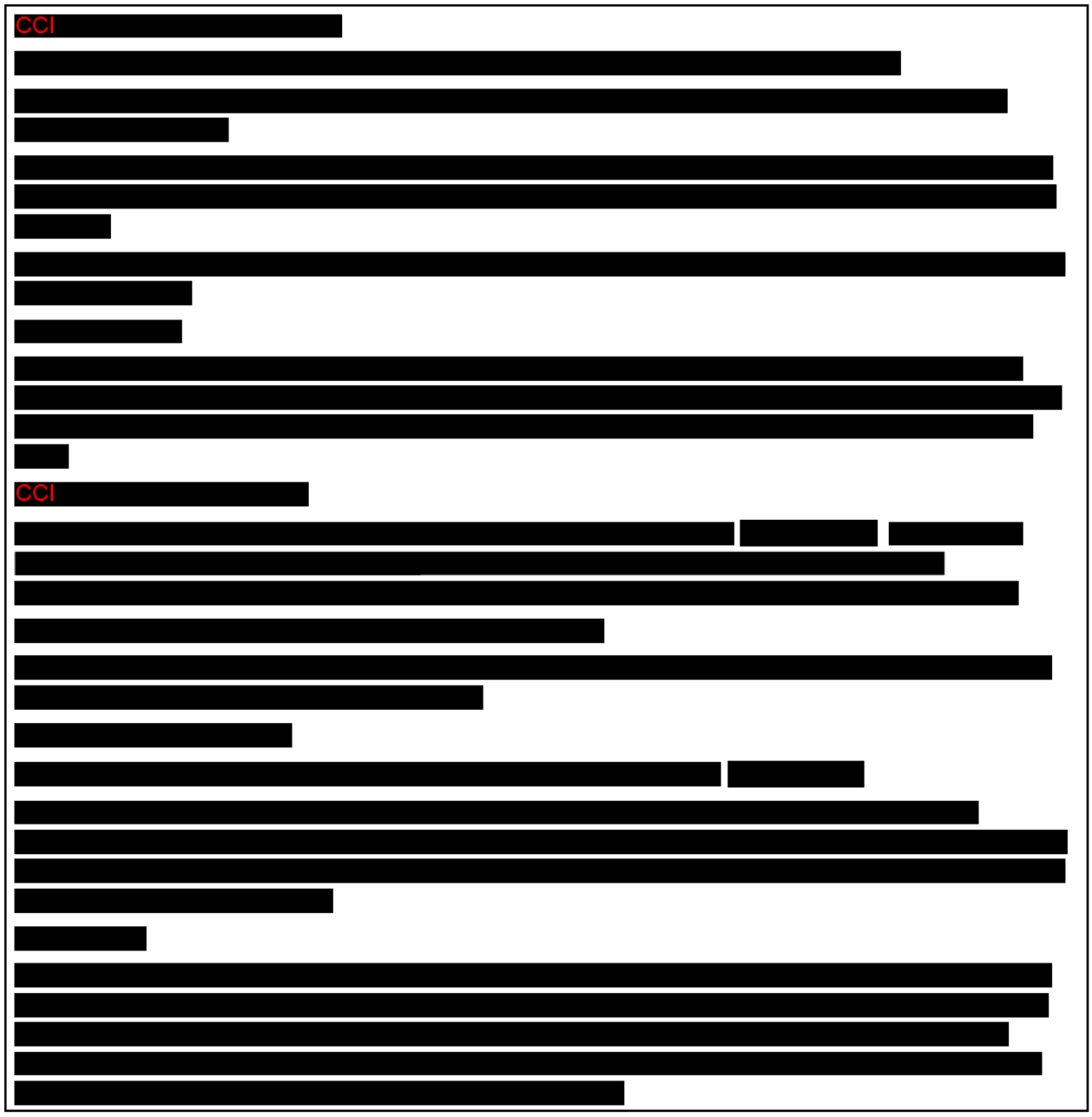
Secondary Efficacy Analysis

The distribution of progression-free survival will be estimated using the Kaplan-Meier method in the modified Safety Analysis Set. Progression-free survival rates at selected time points will be estimated by the Kaplan-Meier method with their 95% CIs using Greenwood's formula. Progression-free survival censoring rule will follow the United States (US) Food and Drug Administration (FDA) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

DOR will be analyzed similarly as PFS. TTR will be summarized using sample statistics, such as sample mean, median, and standard deviation. Only subjects who have achieved an objective response will be included in the analysis of DOR and TTR.

Complete Response rate will be summarized in the modified Safety Analysis Set. Its Clopper-Pearson 95% CI will be calculated.

Independent Review Committee assessment per the Lugano Classification (Cheson et al, 2014) will be used in the primary and secondary efficacy analyses.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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
CCI	[redacted]
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
CCI	[redacted]
Auto-SCT	Autologous stem cell transplant
CCI	[redacted]
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BOR	Best overall response
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
cHL	Classical Hodgkin lymphoma
CD	Cluster of differentiation, such as CD4, CD8, etc.
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CCI	[redacted]
CNS	Central nervous system
CMR	Complete metabolic response
CR	Complete response
CRF	Case report form, paper or electronic
CRO	Contract research organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
DOR	Duration of response
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation	Definition
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
EOS	End of study
EOT	End of Treatment
ESR	Erythrocyte sedimentation rate
Fc	Fragment crystallizable region
FcγR	Gamma Fc receptor
FDA	Food and Drug Administration
FDG-PET	[^{18}F] fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FIH	First in human
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-monocyte colony stimulating factor
GMP	Good Manufacturing Practice
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C antibody
HDT	High dose chemotherapy
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HNSCC	head and neck squamous cell carcinoma
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN-α	Interferon-alpha
IFN-γ	Interferon-gamma
CCI	[redacted]
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International Normalized Ratio

Abbreviation	Definition
irAE	Immune-related adverse event
IRC	Independent Review Committee
IV	Intravenous
LDCHL	Lymphocyte depleted classical Hodgkin lymphoma
LDH	Lactate dehydrogenase
LRCHL	Lymphocyte-rich classical Hodgkin lymphoma
CCI	[redacted]
MCCHL	Mixed cellularity classical Hodgkin lymphoma
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
MMR	Mediastinal mass ratio
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ng	Nanogram
NK	Natural killer
NLPHL	Nodular lymphocyte-predominant Hodgkin lymphoma
NSAID	Nonsteroidal anti-inflammatory drugs
NSCHL	Nodular sclerosis classical Hodgkin lymphoma
NSCLC	Non-small cell lung carcinoma
NYHA	New York Heart Association
ORR	Overall response rate
OTC	Over-the-counter
C	[redacted]
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase Chain Reaction
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Program Death Ligand-1, Programed Death Receptor Ligand-1, Programed Death-1 Ligand-1
PD-L2	Program Death Ligand-2

Abbreviation	Definition
PET	Positron Emission Tomography
PFS	Progression-Free Survival
pH	Pouvoir hydrogene
C	[redacted]
PR	Partial Response
PP	per-Protocol Analysis Set
PT	Prothrombin time
QD	Once daily
Q2W	Once every two weeks
Q3W	Once every three weeks
QC	quality control
QTcF	QT interval corrected using Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
RS	Reed-Sternberg
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMC	Safety Monitoring Committee
SOC	System organ class
SOPs	Standard operating procedures
SPD	Sum of the product of the longest diameters
Stanford V	Doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone
$T_{1/2}$	half-life
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TGF-β	Transforming growth factor-beta
TIL	Tumor-infiltrating lymphocytes
TK	Toxicokinetics
TNF-α	Tumor necrosis factor-alpha
Treg	Regulatory T
TSH	Thyroid stimulating hormone
TTR	Time to response
µg	Microgram
ULN	Upper Limit of Normal
US	United States

Abbreviation	Definition
C	[redacted]
WBC	White blood cell
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

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) classification divides HL into 2 main types: classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL), with cHL further subdivided into nodular sclerosis cHL (NSCHL), mixed cellularity cHL (MCCHL), lymphocyte-depleted cHL (LDCHL), and lymphocyte-rich cHL (LRCHL). Classical HL accounts for 95% and NLPHL accounts for 5% of all HL (Weber et al, 2015). Nodular sclerosis cHL tends to affect young adults more often than the elderly, and is more common in females than males. It is also less frequently associated with Epstein-Barr virus (EBV). Compared to other types of cHL, mediastinal involvement is more common for NSCHL. In contrast to NSCHL, MCCHL and LDCHL are associated with a greater prevalence in males, frequent EBV infection of the neoplastic cells, and tend to exhibit a different pattern of spread within the immune system (Marafioti et al, 2000). MCCHL represents most cases of cHL in the pediatric population, and is typically associated with more advanced stage of disease at presentation and a worse prognosis. For LDCHL, it mainly occurs in an older patient population and in those with acquired immune deficiency syndrome.

Presence of malignant multinucleated Reed-Sternberg (RS) cells, which are of follicular center B-cell origin and constitute less than 1% of cells in the affected lymph nodes, within a characteristic reactive cellular background of normal lymphocytes, eosinophils and histiocytes, is the hallmark of cHL (McDermott et al, 2013). Despite the B-cell origin, RS cells have a global loss of B-cell gene expression and neither produce immunoglobulin nor have functional B-cell antigen receptors (Marafioti et al, 2000). A variety of 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 predominantly comprises Th2 and regulatory T (Treg) cells, and generally lacks Th1 cells, CD8 cytotoxic T cells and natural killer (NK) 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), presence of poor prognostic features, presence of constitutional symptoms, and presence of bulky disease. Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning plays a role in decisions to complete therapy as planned, or to add or omit components of therapy. In general, patients with early stage disease are treated with combined modality strategies using abbreviated course of chemotherapy followed by involved field radiation, while those with advanced stage disease receive a longer course of chemotherapy. Front line chemotherapy regimens for cHL may include doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), or doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, prednisone (Stanford V), with addition of rituximab to chemotherapy for NLPHL (Ansell, 2012).

Despite a high cure rate with initial therapy, approximately 5-10% of HL patients will have primary refractory disease, and 10-30% of patients will relapse after achieving an initial CR (Ansell, 2012). CCI [redacted] Additional therapeutic options include brentuximab vedotin, 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 treatment of patients with relapsed HL after failure of auto-SCT or after failure of at least two prior chemotherapy regimens in patients who are not transplant candidates. Brentuximab vedotin has not been approved in China to date. Nivolumab, a fully human monoclonal immunoglobin G4 (IgG4) antibody directed against programmed cell death-1 (PD-1), has also been approved for treatment of patients with cHL that relapsed or progressed after HDT/auto-SCT and post-transplantation brentuximab vedotin. Nivolumab has not been approved in China. Panobinostat, a histone deacetylase inhibitor (Younes, 2012b), as well as the raptor mammalian target of rapamycin inhibitor everolimus (Johnston et al, 2010), and the immunomodulatory agent lenalidomide (Fehniger et al, 2011), have also been examined in the treatment of relapsed/refractory HL.

1.2. Immune Checkpoint Inhibitors

Immune check point-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 immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor (TCR) and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes (TIL), while the expression of PD-1 ligand, 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 antibody, has been approved by the US FDA for the treatment of patients with unresectable or metastatic melanoma, metastatic non-small cell lung carcinoma (NSCLC) whose tumors express PD-L1 and have progressed on or after platinum-containing chemotherapy, and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that progressed on or after platinum-containing chemotherapy. Pembrolizumab has been shown to be efficacious in both ipilimumab-naïve and ipilimumab-refractory melanoma patients, with ORR of 33-34% and 21-25%, respectively. For NSCLC that progressed after platinum-containing chemotherapy, ORR was 41% while for HNSCC, ORR was 16% with 5% complete responses (Keytruda® US Prescribing Information).

In a study of 31 subjects with cHL (71% of whom had undergone prior auto-SCT) who received pembrolizumab after brentuximab vedotin failure, ORR was 65% with a CR rate of 16% and PR rate of 48%. Majority of responses (70%) lasted longer than 24 weeks with a median follow-up of 17 months. Progression-free survival was 69% at 24 weeks and 46% at 52 weeks. For the subset of subjects who had undergone auto-SCT (n=22), 14% achieve CR and 59% achieved PR for an ORR of 73% for those 22 subjects (Armand et al, 2016).

1.2.2. Nivolumab

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

In a study of 95 subjects with cHL who had previously undergone HDT/auto-SCT and brentuximab vedotin treatments (median of 5 prior systemic regimens), nivolumab was associated with an ORR of 65% with 7% CR and 58% PR. Median duration of response was 8.7 months and TTR was 2.1 months (Opdivo® US Prescribing Information). In another study of 23 HL subjects (78% had received prior brentuximab vedotin, 78% had previously undergone HDT/auto-SCT), ORR was 87% with 17% CR and 70% PR (Ansell et al, 2015).

1.2.3. Immune-related Adverse Events

Immune-related toxicities may develop during immunotherapy treatment. For nivolumab, the majority of immune-related toxicities occur within the first 4 months (Brahmer et al, 2015; Younes et al 2012a). Median time to onset of treatment-related adverse events can vary depending on the type of toxicity: from 5 weeks for skin AEs to 15.1 weeks for kidney AEs. Based on this median time to onset, immune-related toxicities could be classified as early (median time to onset < 2 months) and late toxicities (median time to onset > 2 months). Early toxicities may include skin (5 weeks), gastrointestinal (7.3 weeks) and hepatic (7.7 weeks) events, whereas late toxicities may include pulmonary (8.9 weeks), endocrine (10.4 weeks) and renal (15.1 weeks) events. However, different toxicities can develop at any time since the confidence interval may vary widely among organs: 0.1–57 weeks for skin; 0.1–37.6 weeks for gastrointestinal (Champiat et al, 2016).

1.3. Tislelizumab

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

1.3.1. Non-Clinical Data of Tislelizumab

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 (SPR). It competitively blocks the binding of both PD-L1 and program 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 (PBMCs). In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models, including human cancer cells (A431) human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 NSCLC models, where the PBMCs were co-injected with the A431 or the tumor fragments (BCCO-028 and BCLU-054) into the immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to effector receptors including FcγRs and C1q by *in vitro* assays and with a low or no antibody-dependent cellular-cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effect in humans. Unlike natural IgG4 antibody, tislelizumab has no observable Fab-Arm exchange activity by the *in vitro* assay, predicting the antibody would be stable *in vivo*, unlikely forming 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. Therefore, cynomolgus monkeys were the relevant species for nonclinical safety evaluation.

A PK study of tislelizumab was conducted in monkeys at single doses of 3, 10, or 30 mg/kg or at a repeat dose of 10 mg/kg weekly for 5 doses via IV infusion. The systemic exposure appeared to increase dose-proportionally without gender difference or accumulation. After single dose administration of 3, 10, or 30 mg/kg, the half-life ($T_{1/2}$) ranged from 74 to 183 hours; maximum observed serum concentration (C_{max}) ranged from 90 to 999 µg/mL, and $AUC_{0\text{-}1008h}$ (area under the concentration-time curve from time zero [pre-dose] to last time of quantifiable concentration) ranged from 12,322 to 163,755 h*µg/mL; volume of distribution (V_d) was low, and ranged from 22 to 52 ml/kg.

A PK bridging study for tislelizumab was conducted in monkeys at a single dose of 10 mg/kg via IV infusion. No marked differences on $T_{1/2}$, C_{max}, area under the concentration-time curve (AUC), V_d, CL and MRT were noted between the two batches.

The $T_{1/2}$ of tislelizumab in monkeys supported once biweekly dosing in the repeat-dose toxicology study with adequate systemic exposure to support toxicology evaluation of tislelizumab. Based on PK results in monkeys, the V_d of tislelizumab in human is expected to be like that in monkeys. The $T_{1/2}$ of tislelizumab in human is expected to be 10-20 days depending on the actual dose levels, which allows multiple-dose treatment of tislelizumab for human with a dosing interval of 14 or 21 days to provide the target systemic exposure at the projected therapeutic dose of 0.5 to 10 mg/kg without excessive drug accumulation.

The toxicity and safety profile of tislelizumab was characterized in single dose toxicology studies in mice and monkeys and in a 13-week repeat dose toxicology study in monkeys. The tissue cross reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The pivotal studies were conducted following Good Laboratory Practice (GLP) regulations. The single dosing regimens were spanned from the intended human doses to 10-fold higher than the

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

No apparent toxicity was noted in both mice and monkeys following a single dose up to 100 mg/kg and in monkeys following a repeat dose up to 30 mg/kg biweekly for 13 weeks. The toxicokinetics (TK) profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional without gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no apparent changes in clinical pathology or histopathology were noted in these studies. CCI [redacted] CCI [redacted]

The tissue cross reactivity of tislelizumab was evaluated in normal human and cynomolgus monkey frozen tissues using the immunohistochemistry (IHC) method, with appropriate positive and negative controls. Under the study conditions, no specific tissue cross reactivity with tislelizumab was noted in both human and cynomolgus monkey tissues. Neither hemolytic effects induced by tislelizumab in the rabbit blood cells nor increment of cytokine release from human whole blood cells after treatment with tislelizumab were observed in *in vitro* evaluations.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assays. Toxicokinetics profile was well characterized with dose proportionally increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity and effect on the systemic exposure. The No Observed Adverse Effect Level (NOAEL) of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support first-in-human (FIH) dose safely and ethically.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of tislelizumab.

1.3.2. Clinical Data of Tislelizumab

Study BGB-A317_001 is a two-stage study consisting of a Phase 1a dose escalation and dose-finding component to establish the maximum tolerated dose (MTD), if any, and recommended phase 2 dose(s) (RP2D) (s), followed by a Phase 1b component to investigate efficacy in select tumor types.

The Phase 1a, Part 1 component is a multiple-dose, dose escalation, first-in-human study. The Phase 1a, Part 2 component evaluates the safety and PK of two dosing schedules once every 2 weeks (Q2W) versus once every three weeks (Q3W) at selected doses. The Phase 1a, Part 3 component evaluates the safety and PK of tislelizumab at flat doses. The primary objective of Phase 1a is to assess the safety and tolerability of tislelizumab in subjects with advanced tumors.

The Phase 1b stage is a multicenter, open-label, multiple-arm, indication expansion study. The primary objective of Phase 1b is to assess the anti-tumor activity of tislelizumab in select tumor types.

1.3.2.1. Safety

1.3.2.1.1. Safety Summary of Study BGB-A317_001 Phase 1a

In Study BGB-A317_001 Phase 1a, Part 1, the maximum administered dose was 10mg/kg Q2W. The maximum tolerated dose was not identified. Only one dose-limiting toxicity (DLT) of Grade 3 colitis occurred with 5mg/kg Q2W. Based on the results of 103 pts in the dose escalation and dose expansion part of the Phase 1A study, 5 mg/kg Q3W was selected to explore tislelizumab activity in the Phase 1B.

As of 13 January 2017, treatment-emergent AEs (TEAEs) assessed as related to tislelizumab by the Investigator occurred in 72% of subjects across all parts of Phase 1a. The most frequently occurring events assessed as related to tislelizumab included fatigue (22%), diarrhoea (14%), pruritus (13%), rash (13%), and nausea (10%). There was no apparent correlation between doses (2 mg/kg, 5 mg/kg, or 10 mg/kg) and incidence or severity of TEAEs, assessed as related to tislelizumab. Eleven of the 111 total subjects (10%) had TEAEs assessed as related to tislelizumab that were ≥ Grade 3 in severity. These included 2 events each of fatigue, diabetic ketoacidosis, and hypotension. Table 1 shows the most frequently occurring TEAEs occurring in ≥ 5% of subjects (6 or more subjects) assessed as related to tislelizumab by the Investigator in Study BGB-A317_001 Phase 1b.

1.3.2.1.2. Safety Summary of Study BGB-A317_001 Phase 1b

Treatment-emergent AEs assessed as related to tislelizumab by the Investigator occurred in 41.8% of subjects in Phase 1b. The most frequently occurring events assessed as related to tislelizumab included fatigue (9%), rash (5%), nausea (5%), and diarrhoea (5%). Ten of the total 189 subjects (5%) had TEAEs assessed as related to tislelizumab that were ≥ Grade 3 in severity. These included 2 events each of pneumonitis, diarrhoea, and colitis. All other TEAEs assessed as related to tislelizumab occurred in single subjects.

Table 1: Treatment-emergent Adverse Events Assessed as Related to Tislelizumab Occurring in ≥ 5% of Patients and Corresponding Related ≥ Grade 3 Incidence in Study BGB-A317_001 - Phase 1b (as of 13 January 2017, N = 189)

	Overall Incidence (All Grades)	≥ Grade 3
System Organ Class Preferred Term	**N = 189** **n (%)**	**N = 189** **n (%)**
Patients with at least one related TEAE	79 (41.8)	10 (5.3)
Skin and subcutaneous tissue disorders		
Rash	10 (5.3)	0 (0.0)
Gastrointestinal disorders		
Nausea	10 (5.3)	1 (0.5)
Diarrhoea	9 (4.8)	2 (1.1)
General disorders and administration site conditions		
Fatigue	17 (9.0)	1 (0.5)

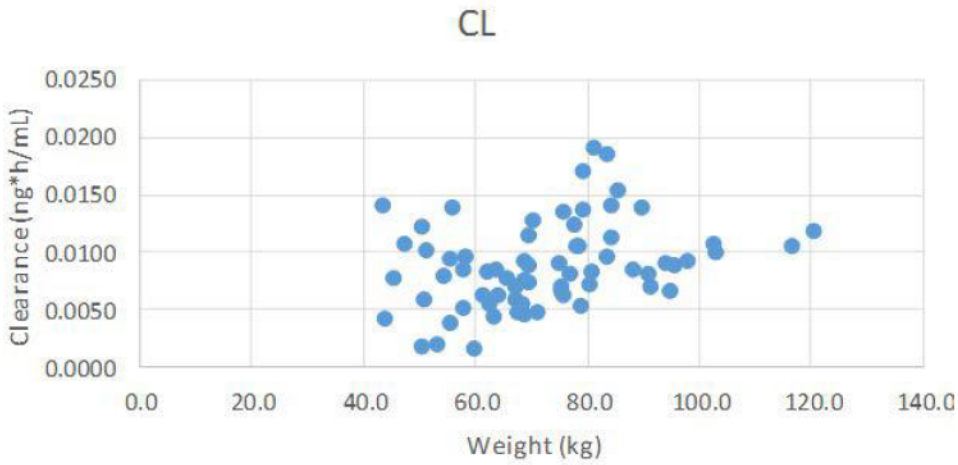
Data as of 13 January 2017; TEAE which starts on or after dosing date, or worsens in severity during treatment relative to the pretreatment state, when the AE is continuous. All AEs are coded using MedDRA version 17.0 or later and graded according to NCI-CTCAE v4.03. A patient with multiple occurrences of an AE is counted only once in the AE category. For the purpose of this reporting, AE occurring at least 9 of 189 patients (numerically, 4.8%) is considered ≥5%.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total patients treated; n = number of patients within each category; NCI-CTCAE = National Cancer Institute Common Terminology Criteria; TEAE = treatment-emergent adverse event.

1.3.2.2. Pharmacokinetics

In the FIH study BGB-A317_001, preliminary PK analysis (with a cut-off date of 18 April 2017) was conducted by non-compartmental analysis methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0 and 10 mg/kg Q2W and patients who received doses of 2.0 and 5.0 mg/kg Q3W (Phase 1a Part 1 and Part 2). The C_{max} and the drug exposure (the area under the 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 and at steady state.

Preliminary population PK analyses (with a cut-off date of 08 October 2016) were conducted using 642 serum samples from 69 patients who received doses of 0.5, 2, 5 and 10 mg/kg Q2W and 2 and 5 mg/kg Q3W. PK from tislelizumab is linear and was characterized with a 2-compartment model with first order elimination. Systemic clearance of tislelizumab was 0.00794 L/h, volume of distribution in the central and peripheral compartment were 2.75 and 1.65 L, respectively, and the terminal elimination half-life was approximately 17 days. Patients' body weight is not a significant covariate on the clearance of tislelizumab (Figure 1), which supports flat-dosing.

Figure 1: Clearance vs Body Weight



1.3.2.3. Anti -tumor Activity

As of 13 January 2017, 111 subjects had received tislelizumab treatment in Phase 1a of Study BGB-A317_001. For the 22 subjects treated in Phase 1a, Part 1, the mean treatment duration was 109.2 days (range: 1 to 365). Duration of treatment was longer for the 81 subjects treated in Phase 1a, Part 2; mean 142.4 days in the 2 mg/kg Q2W and mean 191.9 days in the 5 mg/kg Q3W (overall range: 1 to 471). For the 8 subjects treated in Phase 1a, Part 3, the mean treatment duration was 54.1 days (range: 32 to 67).

For subjects in Phase 1a, Part 1 (n=22), there was 1 subject with a clinical response (confirmed PR) in the 2 mg/kg dose group (5%). For subjects in Phase 1a, Part 2 (n=81), there was 1 subject (1%) with a CR in the 2 mg/kg Q2W dose group and 15 subjects (19%) with confirmed PR (overall clinical response rate: 15% [95% confidence interval [CI]: 5.71%, 29.84%] for the Q2W regimen; and 24% [95% CI: 12.36%, 40.30%] for the Q3W regimen).

There were 155 evaluable subjects and 6 subjects with a confirmed clinical response of PR (4% [95% CI: 1.43%, 8.23%]) in Phase 1b.

1.3.3. Study Rationale

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, The Declaration of Helsinki and any applicable regulatory requirements.

With the detection of PD-L1 over-expression in HL cells which may impart a genetically determined vulnerability of the lymphoma cells to PD-1 blockade (Ansell et al, 2015), coupled with the data of nivolumab in patients with relapsed or refractory HL as described in Section 1.2, the efficacy and safety of tislelizumab in subjects with relapsed or refractory cHL will be investigated. Rationale for this study is further supported by *in vivo* tumor growth inhibition studies which demonstrated tislelizumab has significantly higher anti-tumor activities than nivolumab or pembrolizumab in mouse models carrying allogenic human cancer cells and PBMCs (BeiGene internal data).

The safety of tislelizumab has been tested across a range of doses in Study BGB-A317_Study_001 (0.5 mg/kg to 10 mg/kg Q2W [N=62]; 2 mg/kg to 5 mg/kg Q3W [N=41]) with no MTD defined at the highest dose examined. Based on recommendation of the Safety Monitoring Committee (SMC), tislelizumab at 5 mg/kg Q3W was selected as the dose for the indication expansion part of Study BGB-A317_Study_001 (Phase 1B). Efficacy has also been demonstrated in 15 of 99 evaluable subjects to date who had been diagnosed with a variety of tumor types and were treated with single agent tislelizumab at doses that ranged from 2 mg/kg to 5 mg/kg administered either Q2W or Q3W. Based on the preliminary efficacy data, no clear dose dependence in efficacy was observed among the different expansion cohorts, including 2 mg/kg or 5 mg/kg, at either Q2W or Q3W regimen. 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 on the clearance of tislelizumab (Figure 1), a fixed dose of tislelizumab at 200 mg Q3W will be explored in this study.

1.3.4. Rationale for Tislelizumab Dosage

The fixed dose of 200 mg was selected on the basis of both nonclinical studies and available clinical data as described below.

No tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assay. No apparent toxicity was noted in both mice and monkeys following a single dose up to 100 mg/kg and in monkeys following a repeat dose up to 30 mg/kg biweekly for 13 weeks. The toxicokinetics (TK) profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional without gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no apparent changes in clinical pathology or histopathology were noted in these studies.

According to the Phase 1A PK data in Australia, serum concentrations of tislelizumab showed linear relationships with doses from 0.5 mg/kg Q2W to 10 mg/kg Q2W. Furthermore, according to the results of population PK analysis, there was no significant correlation between the weight of subjects and the *in vivo* clearance rate of tislelizumab. This conclusion supports the hypothesis of fixed dose administration. A 200 mg fixed-dose (body weight adjusted dose between 3 mg/kg and 4 mg/kg) administered every 3 weeks was expected to result in serum exposure that fall between exposures associated between 2 mg/kg and 5 mg/kg doses.

Rates of treatment-emergent, treatment-related AEs as well as treatment-related serious adverse events (SAEs) observed in patients taking 2 mg/kg and 5 mg/kg were comparable suggesting no clear dose dependence across these doses. Consequently, patients receiving 200 mg Q3W fixed dose are expected to have similar AE profiles to those who treated with 2 mg/kg and 5 mg/kg Q3W regimen.

Confirmed overall response rates in patients treated with 2 mg/kg and 5 mg/kg Q2W ranged between 5 and 14%, whereas they were between 17 to 37% for patents dosed 2 mg/kg and 5 mg/kg Q3W. Therefore, clinical activity of tislelizumab is expected to be maintained in patients receiving 200 mg Q3W.

In summary, 200 mg Q3W was selected as the recommended dose for pivotal studies based on the totality of evidence available, including clinical PK, safety, and efficacy

All available PK, safety, and efficacy data for tislelizumab will continue to be evaluated as described above to support the proposed 200 mg fixed dose.

2. OBJECTIVES

2.1. Primary Objective

To evaluate the efficacy of tislelizumab, assessed by Independent Review Committee (IRC), in subjects with centrally confirmed relapsed or refractory cHL, as measured by ORR per the Lugano Classification (Cheson et al, 2014) (Appendix 6).

2.2. Secondary Objectives

To evaluate tislelizumab with respect to:

- Progression-free Survival (PFS) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Duration of Response (DOR) assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Rate of CR assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Time to Response assessed by IRC per the Lugano Classification (Cheson et al, 2014) (Appendix 6)
- Safety and tolerability

2.3. CCI

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- ORR is defined as the proportion of subjects who achieves a best response of CR or PR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).

3.2. Secondary Endpoints

- PFS is defined as the time from the first dose of tislelizumab to the date of PD or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- DOR is defined as the time from the date that response criteria are first met to the date that PD is objectively documented or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- Rate of CR is defined as the proportion of subjects who achieve a best response of CR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- TTR is defined as the time from the date of the first dose of tislelizumab to the time the response criteria are first met, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- To evaluate the safety and tolerability of tislelizumab, as defined by:
  - The incidence and severity of adverse events according to NCI-CTCAE v4.03
  - Changes in vital signs, physical findings, and clinical laboratory results

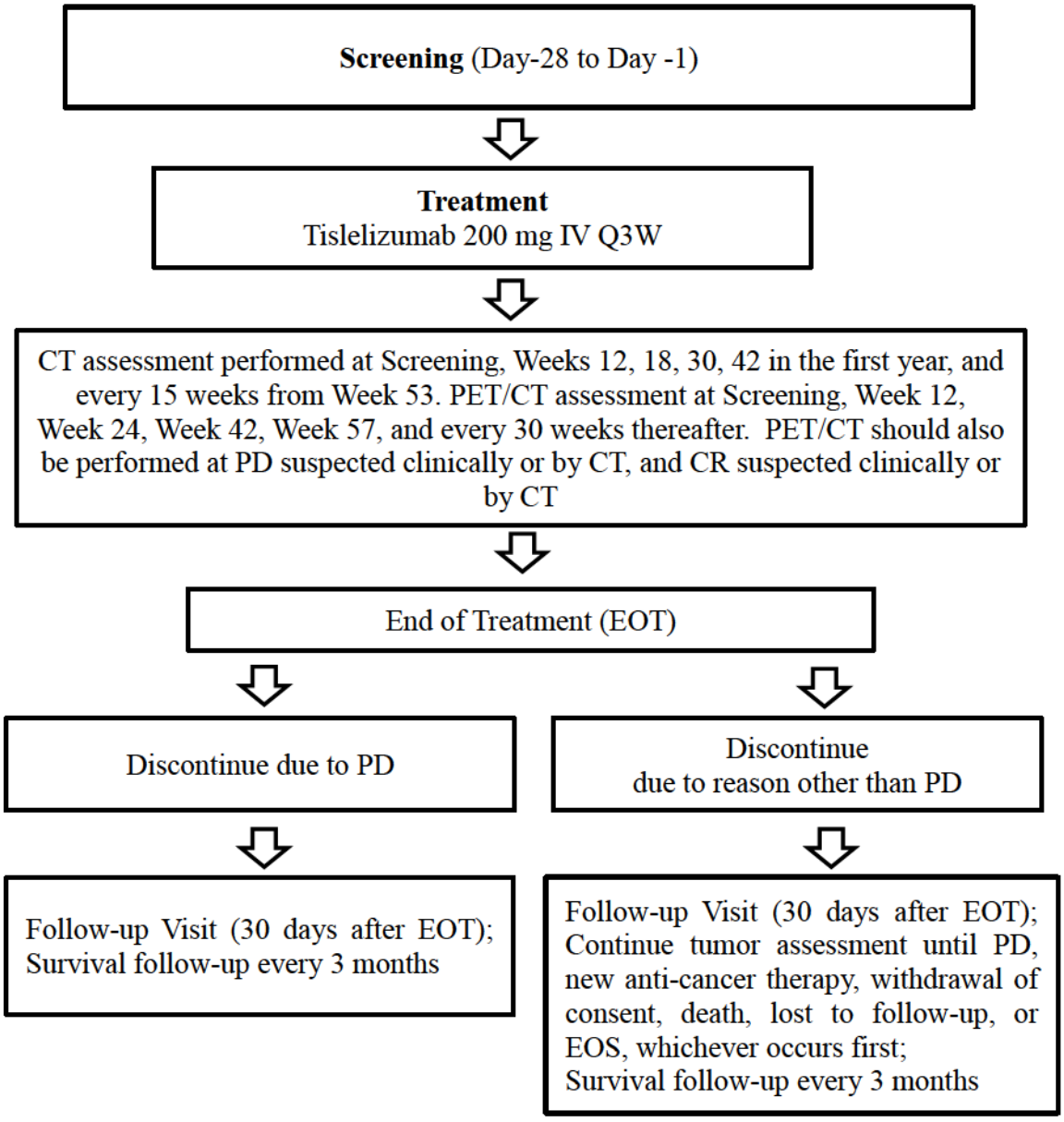
3.3. CCI

4. STUDY DESIGN

This is an open-label, multi-center, single-arm Phase 2 study to evaluate tislelizumab therapy in adult subjects with relapsed or refractory cHL. Subjects must have either failed to achieve a response or progressed after auto-SCT, or are not candidates for auto-SCT secondary to chemo-resistant disease, advanced age (≥ 65 years), or co-existing medical conditions and have received at least two prior systemic chemotherapy regimens for cHL.

Approximately 68 subjects will be enrolled onto study to receive tislelizumab at a dose of 200 mg IV Q3W. Study treatment will continue until PD, unacceptable toxicity, death, or study withdrawal for other reasons. Study design is depicted in Figure 2.

Figure 2: Study Design



Abbreviations: CR, complete response; CT, computed tomography; EOS, end of study; EOT, end of treatment; IV, intravenous; PD, progressive disease; PET, positron emission tomography; Q3W, once every 3 weeks.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects may be enrolled on study only if they meet all the following criteria:

1. ≥ 18 years of age at time of informed consent.
2. Histologically confirmed relapsed or refractory cHL (biopsy from diagnosis or at any relapse is acceptable).
3. Subject must have relapsed (disease progression after most recent therapy) or refractory (failure to achieve CR/CMR or PR to most recent therapy) cHL and meets either one of the following criteria:
   a. Has failed to achieve a response or progressed after auto-SCT.
   b. Has received at least two prior systemic chemotherapy regimens for cHL and is not an auto-SCT candidate due to: chemo-resistant disease (unable to achieve CR or PR to salvage chemotherapy), advanced age (≥ 65 years of age), failure to collect stem cells or unable to perform stem cell collection as assessed by the Investigator, or any significant co-existing medical conditions.
4. Subject must have measurable disease defined as ≥ 1 nodal lesion that is > 1.5 cm in the longest diameter, or ≥ 1 extra-nodal lesion (e.g. hepatic nodules) that is > 1 cm in the longest diameter.
5. Availability of archival or fresh tumor tissue sample from an evaluable core or excisional biopsy (10-15 unstained formalin-fixed paraffin embedded [FFPE] slides). Otherwise, subjects may be permitted to enroll on a case-by-case basis after discussion with the Sponsor's medical monitors, provided cHL diagnosis can be confirmed by a central laboratory.
6. ECOG performance status of 0 or 1.
7. Life expectancy ≥ 12 weeks.
8. Subject must have adequate organ functions as indicated by the following laboratory values:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, independent of growth factor support within 7 days of first dose.
   b. Platelet ≥ 75 x 10^9/L, independent of growth factor support within 7 days of first dose.
   c. Hgb ≥ 8 g/dL or ≥ 5 mmol/L.
   d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN).
   e. AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN, or ≤ 5 x ULN if liver metastases are present.
   f. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin level < 4 x ULN for subjects with Gilbert's syndrome).

9. International normalized ratio (INR) ≤ 1.5 x ULN and aPTT ≤ 1.5 x ULN, unless patient is receiving anticoagulant therapy and coagulation parameters (PT/INR and aPTT,) are within intended therapeutic range of intended use of the anticoagulant at time of Screening. Patients with factor inhibitors prolonging PT or INR may be included after discussion with the medical monitor.
10. Subject must have no evidence of dyspnea at rest and a pulse oximetry of > 92% while breathing room air.
11. Subject must have FEV1/ FVC > 60% by PFT; DLCO, FEV1 and FVC all > 50 % predicted value; all PFTs must be obtained within 4 weeks prior to the first dose of tislelizumab.
12. Female subject is eligible to enter and participate in the study if she is of:
    a. Non-childbearing potential (i.e. physiologically incapable of becoming pregnant) including any female who:
        i. Has had a hysterectomy.
        ii. Has had a bilateral oophorectomy (ovariectomy).
        iii. Has had a bilateral tubal ligation.
        iv. Is post-menopausal (total cessation of menses for ≥ 1 year).
    b. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and for at least 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test within 7 days of the first dose of study drug. Adequate contraception, when used consistently and in accordance with both the product label and instructions of the physician, are defined as:
        i. Vasectomized partner who is sterile prior to the female subject's study entry and is the sole sexual partner for that female.
        ii. Any intrauterine device with a documented failure rate of < 1% per year.
        iii. Double barrier contraception defined as condom with spermicidal jelly, foam, suppository, or film; OR diaphragm with spermicide; OR male condom and diaphragm.
13. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of tislelizumab.
14. Prior chemotherapy, radiotherapy, immunotherapy or investigational therapy (including Chinese herbal medicine and Chinese patent medicine) used to control cancer including locoregional treatment must have been completed ≥ 4 weeks before the first dose of tislelizumab, and all treatment-related adverse events are stable and have either returned to baseline or Grade 0/1 (except for alopecia and hemoglobin). For hemoglobin, please follow inclusion criteria #8c (hemoglobin).
15. Subject has voluntarily agreed to participate by giving written informed consent.

5.2. Exclusion Criteria

Subjects will not be enrolled on study if they meet any of the following criteria:

1. Nodular lymphocyte-predominant Hodgkin lymphoma or gray zone lymphoma.
2. Prior allogeneic hematopoietic stem cell transplant.
3. History of severe hypersensitivity reaction to monoclonal antibodies.
4. 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.
5. 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 or breast.
6. Prior therapy targeting PD-1 or PD-L1.
7. Subject with active autoimmune disease or history of autoimmune disease with high risk of recurrence including but not limited to history of immune-related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barrè syndrome, myasthenia gravis, systemic lupus erythematosus (SLE), connective tissue disease, scleroderma, inflammatory bowel disease including Crohn's disease and ulcerative colitis, autoimmune hepatitis, toxic epidermal necrolysis (TEN), or Stevens-Johnson syndrome.

   Note: Subject is permitted to enroll if he/she has vitiligo, eczema, type I diabetes mellitus, endocrine deficiencies including thyroiditis managed with replacement hormone and/or physiologic corticosteroid. Subjects with rheumatoid arthritis and/or other arthropathies, Sjögren's syndrome or psoriasis controlled with topical medication, and subject with positive serology such as positive antinuclear antibody (ANA) or anti-thyroid antibody should be evaluated for presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
8. Conditions requiring systemic treatment with either corticosteroids (> 10 mg daily Prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of tislelizumab.

   Note: Adrenal replacement doses of ≤ 10 mg daily Prednisone equivalent are permitted in the absence of active autoimmune disease. Topical, ocular, intra-articular, intra-nasal and inhalational corticosteroid (with minimal systemic absorption), a brief course of corticosteroid for prophylaxis (e.g. contrast dye allergy) or for treatment of non-autoimmune conditions (e.g. delayed-type hypersensitivity reaction caused by contact allergen) are allowed.
9. Has history of interstitial lung disease or non-infectious pneumonitis or has evidence of interstitial lung disease or non-infectious pneumonitis.
10. QTcF interval > 480 msec, unless secondary to bundle branch block.
11. Serious acute or chronic infection requiring systemic therapy.
12. Known CNS lymphoma.

13. Underlying medical conditions that, in the Investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events.

14. Known human immunodeficiency virus (HIV) infection, or active hepatitis B (HBV) or hepatitis C (HCV) infection (detected positive by polymerase chain reaction [PCR]).

<table>
<tr><th></th><th colspan="2">Inclusion</th><th colspan="2">Exclusion</th></tr>
<tr><td>HIV</td><td colspan="2">Antibody (-)</td><td colspan="2">Antibody (+)</td></tr>
<tr><td rowspan="2">HBV</td><td colspan="2">HBsAg (-) and HBcAb (-)</td><td colspan="2">HBsAg (+)</td></tr>
<tr><td>HBsAg (-) AND HBcAb (+)</td><td>HBV DNA < 1000 IU/ml. After enrollment, monthly monitoring for HBV DNA or anti-viral therapy should be given to prevent HBV reactivation</td><td>HBsAg (-) AND HBcAb (+)</td><td>HBV DNA ≥ 1000 IU/ml</td></tr>
<tr><td rowspan="2">HCV</td><td colspan="2">HCV Ab (-)</td><td rowspan="2">HCV Ab (+)</td><td rowspan="2">HCV RNA ≥ 1 (log_{10} IU/ml)</td></tr>
<tr><td>HCV Ab (+)</td><td>HCV RNA < 1 (log_{10} IU/ml)</td></tr>
</table>

HBsAg: Hepatitis B surface antigen; HBcAb: Hepatitis B core antibody; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HCV Ab: Hepatitis C antibody; HIV: human immunodeficiency virus; DNA: deoxyribonucleic acid; RNA: ribonucleic acid

15. Autologous hematopoietic stem cell transplant within 100 days of first dose of tislelizumab.

16. Use of any live vaccine against infectious diseases (e.g. 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.

17. Major surgery within 4 weeks of the first dose of tislelizumab.

18. Pregnant or lactating women.

6. STUDY TREATMENTS

6.1. Study Treatment

Subjects will receive tislelizumab at 200 mg IV Q3W. One cycle is 21 days. All patients should not receive premedication to prevent infusion reaction before the first infusion of tislelizumab, in order to determine if premedication is necessary. If a patient experiences an infusion reaction, he/she may receive premedications on subsequent dosing days. The premedications should be chosen per institutional standard of care, at the discretion of the treating physician.

6.2. Study Treatment Preparation and Dispensation

6.2.1. Packaging and Labeling

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, USP type I), 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. One vial is packaged in a single carton box.

The label will include, at minimum, drug name, dose strength, contents, sponsor, protocol number, lot number, directions for use, storage conditions and caution statements. The contents of the label will be in accordance with all applicable regulatory requirements.

6.2.2. Handling and Storage

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.

Investigational product must be dispensed or administered per procedures described herein. Only subjects 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.

Refer to the Pharmacy Manual for details regarding administration, accountability, and disposal.

6.2.3. Compliance and Accountability

Compliance will be assessed by the Investigator and/or study personnel at each visit and information provided by the subject and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each subject visit.

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or administered to and returned by subjects, if applicable.

6.2.4. Disposal and Destruction

After completion of the study, all unused tislelizumab will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies will be returned to the sponsor or destroyed on site or depot, after receiving written sponsor approval.

6.3. Subject Numbering and Treatment Assignment

6.3.1. Subject Numbering

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned when the subject is screened or enrolled in the study. Subject numbers will be assigned in chronological order starting with the lowest number. Once a subject number has been assigned to a subject, it cannot be reassigned to any other subject.

6.3.2. Treatment Assignment

All subjects in the study will receive tislelizumab.

6.3.3. Treatment Blinding

This is an open-label study.

6.4. Dosage and Administration

Tislelizumab at 200 mg will be administered by IV infusion using a volumetric pump through an IV line containing a sterile, non-pyrogenic, low-protein binding < 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, subjects who receive the first and second infusion of tislelizumab must be observed for 2 hours after infusion, and that resuscitation equipment and emergency agents need to be available.

For more detailed information regarding administration, refer to the Pharmacy Manual and Investigator's Brochure.

The initial infusion will be delivered over 90 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 60 min, over 30 min if 60 min infusion tolerated. Do not co-administer other drugs through the same infusion line.

6.5. Dose Interruption and Modification

6.5.1. Dose Modification

There is no dose reduction or dose escalation of tislelizumab.

6.5.2. Dose Interruption

Immune-related adverse event (irAE), as described in Section 1.2.3., may occur during treatment with checkpoint inhibitors such as tislelizumab. Key points in the event of an irAE:

- Close monitoring
- Ambulatory versus inpatient care
- Symptomatic treatment
- Immunotherapy suspension or termination
- Corticosteroid therapy and associated measures
- Other immunosuppressive drugs
- Patient information on how to self-monitor clinical elements

Refer to Section 9.1.12.2 and Appendix 8 for information regarding the management of irAEs.

6.6. Dose Delay

Dose delay criteria apply for all drug-related AEs. The subjects should resume tislelizumab treatment as soon as possible after the AEs recover to normal or Grade 1 within 12 weeks after last dose of study treatment. In case a subject is benefiting from the study treatment while meeting the discontinuation criteria, discussion between Sponsor and Investigator will be conducted to make a decision that will be in the best interest of the subject.

Subjects with infusion delay > 6 weeks from planned dosing date for reason(s) other than treatment-related toxicity should normally discontinue treatment and enter the Follow-up Period except for delays related to prophylactic vaccinations or after specific consultation and agreement between the Investigator and Sponsor medical monitor in settings where benefit/risk may justify continued study therapy (e.g. subject deriving clinical benefit who requires prolonged steroid taper for management of irAEs).

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 5), with subsequent visits conducted according to the planned schedule Q3W from Cycle 1 Day 1.

6.7. Concomitant Medications and Non-Drug Therapies

6.7.1. Prohibited Medications

The following medications are prohibited during Screening and Study Treatment Periods:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroid > 10 mg daily Prednisone equivalent (except to treat a drug-related adverse event).

- Any concurrent antineoplastic therapy (i.e. 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 therapy and while participating in study. Examples of live vaccines include but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine. Inactivated influenza vaccine is allowed.
- Chinese herbal medicine and Chinese patent medicine for treatment of cancer.

6.7.2. Permitted Medications

In general, concomitant medications and therapies deemed necessary for supportive care (e.g. anti-emetics, anti-diarrheals) 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 medication will be recorded on the electronic case report form (eCRF) including all prescription and over-the-counter (OTC) medications, herbal supplements, and IV 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 mediation and 30 days after the last infusion of study medication should be recorded.

Systemic corticosteroids required for the control of irAEs must be tapered over at least 1 month and be at non-immunosuppressive doses (≤ 10 mg/day of Prednisone or equivalent) before the next study drug administration. The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

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

6.8. Diet/Activity/Other Considerations

6.8.1. Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.8.2. Contraception

Tislelizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if tislelizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive or of non-childbearing potential (i.e. physiologically incapable of becoming pregnant).

Highly unlikely to conceive or of non-childbearing potential (i.e. physiologically incapable of becoming pregnant) is defined as 1) has had a hysterectomy, or 2) has had a bilateral oophorectomy (ovariectomy), or 3) has had a bilateral tubal ligation, or 4) is postmenopausal (total cessation of menses for ≥ 1 year). 1) or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use two methods of birth control (which is also recommended for the female partners of male patients).

Subjects must agree to use adequate contraception while on study treatment, defined as vasectomized partner who is sterile prior to the female subject's study entry and is the sole sexual partner for that female, any intrauterine device with a documented failure rate of < 1% per year, or double barrier contraception defined as two birth control methods, e.g. two barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through 120 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. To participate in the study, they must adhere to the contraception requirement (described above) for the duration of the study and follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not enter the study.

6.8.3. Pregnancy

Tislelizumab may have adverse effects on a fetus; therefore, women with a positive pregnancy test at Screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with tislelizumab, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the sponsor. The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the sponsor and followed as described above.

6.8.4. Nursing Women

It is unknown whether tislelizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

6.9. End of Treatment

All subjects, regardless of reason for discontinuation of study treatment, will undergo an End of Treatment (EOT) visit within 7 days of stopping study drug. The reason for discontinuation from treatment will be recorded on eCRF. Refer to Section 7.1.4 for required assessments at the EOT visit.

Subjects may discontinue study drug for any of the following reasons:

- Disease progression
- Adverse event(s)
- Subject withdrew consent
- Investigator decision
- Other

Subjects may voluntarily withdraw consent from study at any time. A subject may continue to participate in the follow up phase if the subject withdraws consent from the treatment phase.

6.10. Follow-up Phase

6.10.1. Safety Follow-up

Subjects 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 study treatment. In addition, telephone contacts with subjects should be conducted to assess AEs and concomitant medications (if appropriate, i.e. associated with an AE or is a new anti-cancer 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.

The EOT visit at which a response assessment showed progressive disease, resulting in subject discontinuation, may be used as the safety follow-up visit, provided that it occurred 30 days (± 7 days) after the last study treatment. Subjects who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.2.

See the study schedule provided in Appendix 5 for assessments to be performed at the safety follow-up visit.

6.10.2. Efficacy Follow Up

Disease status for subjects who discontinue from study drug for any reason other than PD (e.g. AE) will be assessed radiographically by the same imaging modality as the Treatment Period. Tumor imaging will be performed per protocol (refer to Section 3, Figure 2 Study Design) until PD, new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or end of study (EOS), whichever occurs first.

6.10.3. Survival Follow Up

Subjects will be followed for survival after safety follow-up visit or efficacy follow-up via phone contact (with the subject's guardian, if applicable) approximately every 3 months. The Investigator or his/her designee will also continue to collect information on new anti-cancer therapy given after the last dose of study drug.

6.11. End of Study

Patients still receiving study treatment when the roll-over study is open will transfer to the roll-over study for continuous treatment and monitoring. Patients already off study treatment but not withdrew the ICF will have efficacy (if discontinuation not due to disease progression), safety and survival follow-up (as defined in this parent study) in the roll-over study (see Appendix 5).

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

- Major protocol violation
- Subject withdrew consent
- Lost to follow-up
- Death
- Study termination by sponsor
- Investigator's discretion

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

Subjects lost to follow-up should be recorded as such on the eCRF. For subjects who are lost to follow-up, the Investigator should document in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc.

7. STUDY ASSESSMENTS

7.1. Study Procedures

7.1.1. Screening

A signed, written informed consent form (ICF) must be obtained from the subject prior to any study-specific procedures or assessments. Re-screening 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).

Procedures and assessments to be performed during the Screening window (Day -28 to Day -1):

- Informed consent
- Demographic
- Medical history including date of cHL diagnosis, date of last recurrence, date of last cancer treatment, cHL subtype, stage of disease at diagnosis (Appendix 3) IPS at diagnosis (Appendix 4), and biopsy details
- Inclusion/Exclusion Criteria
- Concomitant medications within 28 days prior to first dose of tislelizumab
- Prior type and dates of treatments for cHL including chemotherapy, radiation, and surgery
- CT with contrast and PET/CT of neck, chest, abdomen, and pelvis. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered. Total body MRI is allowed if contraindicated to CT with contrast.
- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry
- Physical examination
- Pulmonary function test
- Adverse events
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA), if not performed within 90 days of first day of Screening
- Complete blood count (CBC) with differential, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW)
- Comprehensive serum chemistry panel (Refer to Appendix 2)

- HBsAg, HBsAb, HBcAb, HCV Ab, and further testing by PCR to assess HBV DNA or, HCV RNA level may be performed for determination of study eligibility as per Inclusion/Exclusion Criteria.
- Coagulation parameters (PT, aPTT, INR)
- Serum pregnancy test (only in women of childbearing potential), must be performed within 3 days of the first dose of tislelizumab
- Archival tumor tissue and/or a fresh tumor biopsy (10 to 15 unstained formalin-fixed, paraffin-embedded [FFPE] slides)
- Bone marrow aspirate and biopsy, if not performed within 60 days of first dose of study drug
- Refer to the Schedule of Assessment (Appendix 5) for additional details.
- The following eCRFs must be completed for screen-fail patients:
- Screening Phase Disposition page (including reason for not being started on treatment)
- Informed consent
- Demography
- Adverse Events (only if an SAE occurs)
- Inclusion/Exclusion criteria

7.1.2. Cycle 1 Day 1 (± 3 days)

Procedures and assessments to be performed on Day 1 of Cycle 1 (± 3 days):

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry
- Height and weight
- Physical examination
- Adverse events
- Concomitant medications
- CBC with differential, MCV, MCH, MCHC, RDW
- Comprehensive serum chemistry panel (Refer to Appendix 2)
- Erythrocyte sedimentation rate (ESR)
- Urinalysis
- Thyroid function test (thyroid stimulating hormone [TSH], free T4, free T3)
- Study drug administration

- CCI [redacted]

Refer to the Schedule of Assessment (Appendix 5) for further details.

7.1.3. Day 1 of Cycle 2 and All Subsequent Cycles (± 3 days)

Procedures and assessments to be performed on Day 1 of Cycle 2 and all subsequent cycles (± 3 days):

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry
- Weight
- Physical examination
- Adverse events
- Concomitant medications
- CBC with differential, MCV, MCH, MCHC, RDW
- Comprehensive serum chemistry panel (Refer to Appendix 2)
- Urinalysis (start at C7D1 and repeat every 6 cycles)
- Study drug administration
- CCI [redacted]

Refer to the Schedule of Assessment (Appendix 5) for further details.

7.1.4. End of Treatment

Procedures and assessments to be performed within 7 days of stopping tislelizumab at EOT:

- ECOG performance status
- Vital signs including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry Physical examination
- Adverse events
- Concomitant medications
- CBC with differential (Refer to Appendix 2)
- Comprehensive serum chemistry panel (Refer to Appendix 2)
- Thyroid function test (TSH, free T4, free T3)
- Urinalysis

- CT with contrast of neck, chest, abdomen, and pelvis. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered. Tumor imaging for EOT does not have to be performed if the most recent tumor imaging was performed within the previous 6 weeks.
- Urine pregnancy test
- Bone marrow aspirate and biopsy will be required for confirmation of CR if baseline bone marrow was positive for cHL involvement.
- PET/CT for confirmation of PD, if PD is reason for discontinuation of treatment.

Refer to the Schedule of Assessment (Appendix 5) for further details.

7.1.5. Safety Follow-up

Procedures and assessments to be performed at the Safety Follow-up Visit (30 days ± 7 days after last dose of tislelizumab):

- Vital signs including temperature, blood pressure, pulse, respiratory rate, and pulse oximetry
- Physical examination
- ECOG performance status
- 12-lead ECG
- Adverse events
- Concomitant medications
- CBC with differential, MCV, MCH, MCHC, RDW
- Comprehensive serum chemistry panel (Refer to Appendix 2)
- Urinalysis
- Thyroid function test (TSH, free T4, free T3)
- CCI

In addition, telephone contacts with subjects should be conducted to assess AEs and concomitant medications (if appropriate, i.e. associated with an AE or is a new anti-cancer 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.

Refer to the Schedule of Assessment (Appendix 5) for further details.

7.1.6. Survival Follow-up

Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow subjects approximately every 3 months for subsequent antitumor treatment after the end of study treatment and survival until subject death or study termination by the Sponsor.

7.2. Tumor Assessment

7.2.1. Imaging Studies

Response assessment for ORR will be by contrast CT and PET/CT separately and categorized as per the Lugano Classification (Appendix 6).

7.2.1.1. CT with contrast

Tumor assessment by CT with contrast of neck, chest, abdomen, and pelvis will be performed at protocol specified time points (Refer to Appendix 5). Total body MRI is allowed if CT with contrast is contraindicated. PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered.

CT scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. 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 from baseline.

7.2.1.2. PET/CT

Tumor assessment by PET/CT will be performed at protocol specified time points (Refer to Appendix 5). PET/CT may be used in lieu of a CT with contrast only if the CT of the PET/CT has been performed with diagnostic quality and contrast is administered.

7.2.2. Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy will be required at Screening. Immunohistochemistry should be performed. Repeat bone marrow aspirate and biopsy is required at the time of CR for confirmation of response if baseline marrow examination was positive for cHL involvement.

7.2.3. Disease Progression with Immune Checkpoint Inhibitors

During treatment with immune checkpoint inhibitors such as with tislelizumab, pseudo-progression may occur due to immune cell infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Subjects are allowed to continue study treatment if there is suspicion of pseudo-progression, provided they are asymptomatic and have radiographic progression only, until a second consecutive CT scan demonstrates PD at which time study treatment will be discontinued permanently. Patients should continue on treatment to progression regardless of response status (e.g. in CR).

7.2.4. Archival Tissue Collection with Central Diagnosis Confirmation

Archival tissue (10-15 unstained FFPE slides) will be collected at Screening. Central review of the tissue will be performed to confirm diagnosis of cHL (central confirmation of cHL diagnosis not required for study entry). Enrollment may be increased based on central review.

7.3. CCI

[redacted]

7.4. Safety and Tolerability Assessments

Safety assessments should be performed at all visits by the Investigator throughout the study. Safety assessments will consist of monitoring all AEs and serious adverse events (SAEs), regular monitoring of blood tests, urine tests, vital signs, weight, and performance status, and by regular physical examinations (PEs). For schedule of study visits, refer to the Schedule of Assessment (Appendix 5).

7.4.1. Adverse Events

All adverse events, including SAEs, will be collected as described in Section 9. At the end of treatment, ongoing adverse events considered related to study treatment will be followed until the event has resolved to baseline, the event is assessed by the investigator as stable, the subject is lost to follow-up, the subject withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

Attention should be focused on identifying potential irAEs and managing these irAEs effectively. The Administrative Binder contains a comprehensive guideline for the assessment and management of irAEs to ensure that potential immune related events are identified in timely manner. Most irAEs expected from immunotherapies, including tislelizumab, are manageable and reversible when detected and managed early.

7.4.2. Physical Examination, Vital Signs, Height, and Weight

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. A complete or targeted physical examination, vital signs (sitting blood pressure, pulse rate, body temperature, and respiratory rate) and weightwill be performed at each study visit. To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is >150/100 mmHg in a patient without a history of hypertension, or increased >20 mmHg

(diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation. Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured on Day 1 of Cycle 1 only. Weight will be measured on Day 1 of each treatment cycle.

Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.4.3. Medical History

The Investigator will obtain the patient's medical history at the Screening Visit. Medical history will include all active conditions, and any conditions diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF.

7.4.4. ECOG Performance Status

Eastern Cooperative Oncology Group performance status (Table 2) will be assessed at the Screening Visit, Day 1 of each treatment cycle, End of Treatment Visit, and at the Safety Follow-up Visit. If the Screening laboratory assessment is performed ≤ 3 days prior to the first administration of tislelizumab, they do not have to be repeated on Day 1 of Cycle 1 and will be used as Baseline.

Table 2: ECOG Performance Status

Grade	Performance
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, e.g. light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

7.4.5. Electrocardiogram

Electrocardiogram (ECG) assessments are to be performed with the subject in semi-recumbent supine position and rested for 5 minutes.

7.4.6. Laboratory Evaluations

Laboratory tests will be collected and analyzed as specified in Appendix 5. Screening blood tests performed within 3 days of the first study drug administration do not need to be repeated on Cycle 1 Day 1. Abnormal laboratory values will constitute 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 AEs eCRF. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g. cause study discontinuation or constitutes in and of itself a SAE) should be recorded on the AEs eCRF. Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

7.4.6.1. Hematology

Hematology laboratory studies include white blood cell (WBC) count with differential (neutrophil, lymphocyte, monocyte, eosinophil, basophil), Hgb, hematocrit, platelet count, and RBC indices. In the event of ≥ Grade 3 neutropenia or thrombocytopenia that developed on study treatment, frequency of CBC monitoring will be conducted as often as clinically indicated, at Investigator's medical judgment, to ensure subject safety, and close monitoring should occur until toxicity resolves to ≤ Grade 2.

7.4.6.2. Clinical Chemistry

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

7.4.6.3. Coagulation

Coagulation profile includes PT, INR, and aPTT will be performed at Screening. Repeat testing may also be performed as clinically indicated during the treatment period including for those subjects receiving anticoagulation therapy at study entry.

7.4.6.4. Urinalysis

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity.

7.4.6.5. Hepatitis B and Hepatitis C Testing

Testing will be performed at Screening and includes HBsAg, HBcAb, HBsAb, HCV Ab, HBV DNA PCR, HCV RNA PCR. Subjects who are HIV Ab or HBsAg positive will be excluded from study entry. Subjects who are HBsAg negative but HBcAb positive, HBV DNA must be < 1000 IU/ml to be eligible for study entry. Subjects who are HCV Ab positive, HCV RNA must be < 1 (log_{10}IU/ml) to be eligible for study entry.

7.4.6.6. Thyroid Function Test

Free T3, Free T4, and TSH will be performed.

7.4.6.7. Pregnancy Test

A serum pregnancy test will be performed at Screening and End of Treatment in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study. Subjects must have a negative serum pregnancy test at Screening (within 3 days before the first investigational product administration). Subsequent tests may be urine tests, and should be performed as clinically indicated. A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

8. DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the Sponsor's or the Contract Research Organization's (CRO's) qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

8.1. Data Collection

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and any data being entered into the system for any subjects.

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by International Conference of Harmonisation (ICH) guidelines, the case report form (CRF) is a printed, optical, or electronic document designed to record all the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

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

8.2. Data Management/Coding

Data generated within this clinical study will be handled per the relevant SOPs of the data management and biostatistics departments.

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data

of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will answer queries sent to the investigator.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives tislelizumab, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique User ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant diseases/medical history will be coded using the MedDRA Version 19.1 or higher.

8.3. Quality Assurance

To ensure compliance with Good Clinical Practice (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.

9. SAFETY MONITORING AND REPORTING

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

9.1. Adverse Events

9.1.1. Definition and Reporting of an Adverse Event

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 an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions 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 (e.g., 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 subject identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.1.2. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v4.03.

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 (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- 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 9.1.8.1.

9.1.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. 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 will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, 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 makes assessment of causality for every SAE prior to transmission of the SAE report/eCRF to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of the follow-up information, amending the SAE report/eCRF accordingly.

Investigators must also systematically assess the causal relationship of AEs to investigational medicinal product (s) (IMP [s])/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions:

- Definitely related: There is clear evidence to suggest a causal relationship that there is reasonable temporal relationship; the positive of de-challenge result (when necessary the positive of re-challenge result); the occurrence of AE that could be attributed to the pharmacological effect of study treatment
- Probably related: This causality assessment will be applied for AE that is regarded by the investigator as highly positive related to the study treatment that: There is a reasonable temporal relationship; the occurrence of AE could not be explained by the subject's medical history, concurrent medical condition, or other the subject's signs or symptoms; the positive of de-challenge result; the positive of re-challenge result.
- Possibly related: There is some evidence to suggest a causal relationship (e.g., 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 (e.g., the subject's clinical condition, other concomitant AEs).
- Unlikely related: There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the AE.
- Unrelated: An AE will be considered "not related" to the use of the product if any of the following tests are met:
  - An unreasonable temporal relationship between administration of the product and the onset on the AE (e.g., the AE occurred either before, or too long after administration of the product for it to be considered product-related);

- A causal relationship between the product and the AE is biologically implausible (e.g., death as a passenger in an automobile accident);
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related AE).

9.1.4. Follow-Up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the sponsor on the subject'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 subject is lost to follow-up or the subject withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, 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 subject 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 will be recorded on the originally completed SAE report/eCRF, with all changes signed and dated by the investigator. The updated SAE report/eCRF should be resent to the sponsor within the time frames outlined in Section 9.1.8.1.

9.1.5. Laboratory Test Abnormalities

Abnormal laboratory findings (e.g., clinical chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 9.1.1) or an SAE (as in Section 9.1.6). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. They should be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, need dose interruption or discontinuation or are clinically significant in the opinion of the investigator.

The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

9.1.6. 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 subject was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: In general, hospitalization signifies that the subject 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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  – Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

  – Hospitalization for social/convenience considerations is not considered an SAE.

  – Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE.
- 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 (e.g., sprained ankle), which may interfere 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 (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

9.1.7.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after the last study treatment of tislelizumab. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

9.1.7.2. Eliciting Adverse Event

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?

9.1.7.3. Specific Instructions for Recording Adverse Events and Serious Adverse Events

9.1.7.3.1. 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 (e.g., 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), unless the signs/symptoms are clinically significant.

9.1.7.3.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (e.g., 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 subject initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

9.1.7.3.3. Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, it should be recorded as a new AE on the eCRF (and a stop date should be recorded in the previous AE).

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

9.1.7.3.4. Disease Progression

Disease progression is measured as an efficacy endpoint and not considered to be an AE. However, if there are separate identifiable clinical sequelae that result from disease progression, those sequelae are reportable as AEs. For instance, a subject with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as "pleural effusion" instead of disease progression or metastasis to lungs. If a subject has a seizure that is determined to be associated with a brain metastasis, the term "seizure" should be recorded as the AE instead of disease progression or brain metastasis. If a subject experienced multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data. They should not be reported as an SAE. If deaths are assessed by the investigator as not solely due to disease progression, whether they are assessed as related or not related to the study drug, they should be reported as an SAE immediately.

If there is any uncertainty regarding whether an AE is due to disease progression, it should be reported as an AE.

9.1.7.3.5. Death

When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death".

9.1.8. Prompt Reporting of Serious Adverse Events

9.1.8.1. Timeframes for Submitting Serious Adverse Events

Serious adverse events will be reported promptly to the sponsor or designee as described in Table 3, once the investigator determines that the AE meets the protocol definition of an SAE.

Table 3: Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial Report	Document	Follow-up SAE	Document
All SAEs	Within 24 hours of first knowledge of the SAE	SAE form	As expeditiously as possible	Updated SAE form

9.1.8.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.1.8.1. The SAE report form will always be completed as thoroughly as possible with all available details of the SAE, signed by the investigator and forwarded to the sponsor within the designated time frames. If the investigator does not have all the information regarding an SAE he/she will not wait to receive additional information before notifying the sponsor of the SAE/AE of special interest and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.8.1.

E-mail transmission of the SAE report form is the preferred method to transmit this information to the project contact for SAE receipt. Facsimile transmission is the back-up method for SAE reporting.

The sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

9.1.8.3. 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 9.1.8. 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. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

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 (IRB)/Independent Ethics Committee (IEC).

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (e.g., revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

9.1.9. Pregnancy Reporting

If a female subject or the partner of a male subject becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab, a pregnancy report form should 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 or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. Pregnancy should be recorded on Pregnant Form in eCRF.

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 subject exposed to the study drug should be recorded and reported as an SAE.

9.1.10. Post-study Adverse Event

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, defined in Section 9.1.7.1.

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

9.1.11. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator immune-related (see Section 9.1.12.2) should be classified as irAEs and identified as such in 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 8.

An extensive list of potential irAEs appears in Section 9.1.12.2, Table 5. 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 8.

9.1.12. Management of AEs 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 1 hour afterwards 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 for infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE criteria are outlined below**.**

9.1.12.1. 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. Subjects should be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) 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 tislelizumab is presented in Table 4.

Table 4: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Tislelizumab

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 or 2 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Tislelizumab infusion rate is decreased by 50% and any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours.	Tislelizumab infusion is discontinued. Infusion is resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least Grade 1 in severity and 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 (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Tislelizumab infusion is immediately discontinued and infusion tubing would be disconnected from the subject. Proper medical management should be instituted as described below. The patient should be withdrawn from tislelizumab treatment.
Grade 4: life threatening Life-threatening consequences; urgent intervention indicated.	Patients have to be withdrawn immediately from tislelizumab treatment and must not receive tislelizumab treatment anymore. Proper medical management should be instituted as described below. Hospitalization is recommended.

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 subject should be withdrawn from tislelizumab treatment.

CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), anti-pyretic (e.g., paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (e.g., diphenhydramine or

equivalent) and an anti-pyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

CTCAE Grade 3 or 4 infusion reaction: Immediately stop the infusion. 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 anti-histamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, tislelizumab must be discontinued.

9.1.12.2. CCI

[redacted]

Table 5: Immune-related Adverse Events

Body System Affected	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, e.g. 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.

Dose modification and management for irAEs are detailed in Appendix 8.

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.

9.1.12.3. Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated glomerular filtration rate [eGFR] > 30 mL/min and < 60 mL/min by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study. The following algorithm is proposed for the use of steroid treatment in the management of irAEs:

- If the serum creatinine is normal at baseline, please see Section 9.1.12.2 and refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values.

- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with tislelizumab, refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. Check the eGFR using Appendix 8 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value or the eGFR falls below 20 mL/min.
- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 8 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the sponsor medical monitor.

9.1.12.4. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (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 (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and 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 infusion must be immediately stopped and the patient discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if a hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and ICU 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 (i.e. 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (i.e. paracetamol) may be given to patients at the discretion of the investigator.

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

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

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the Tislelizumab Investigator's Brochure.

9.1.14. Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

9.2. Safety Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an internal Safety Monitoring Committee (SMC).

The first SMC safety review will occur after at least 20 patients have been on treatment for at least one month in order to determine if the proposed dosing schedule of tislelizumab is safe and tolerable. The SMC may recommend study modification including termination of the study due to safety and/or efficacy concerns. The function and membership of the SMC will be described in the SMC Charter.

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

Following SMC review and discussion, the Sponsor will make all final decisions regarding any change in study conduct. Please see the details in the SMC Charter.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per Sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

10.1. Primary, Secondary and CCI Study Endpoints

10.1.1. Primary Endpoint

- ORR is defined as the proportion of subjects who achieves a best response of CR or PR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).

10.1.2. Secondary Endpoints

- PFS is defined as the time from the first dose of tislelizumab to the date of PD or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- DOR is defined as the time from the date that response criteria are first met to the date that PD is objectively documented or death, whichever occurs first, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- Rate of CR is defined as the proportion of subjects who achieves a best response of CR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- TTR is defined as the time from the date of the first dose of tislelizumab to the time the response criteria are first met, assessed by IRC per the Lugano Classification (Cheson et al, 2014).
- To evaluate the safety and tolerability of tislelizumab, as defined by:
  - The incidence and severity of adverse events according to NCI-CTCAE v4.03
  - Changes in vital signs, physical findings, and clinical laboratory results

10.1.3. CCI

[redacted]

- CCI [redacted]

[redacted]

10.2. Statistical Analysis

10.2.1. Analysis Sets

The Safety Analysis Set includes all subjects who received any dose of tislelizumab. This will be the population for the safety analyses.

The modified Safety Analysis Set includes all subjects in the Safety Analysis Set who had confirmed cHL. This will be the population for the efficacy analyses.

The Per-Protocol (PP) Analysis Set includes subjects who received any dose tislelizumab and had no major protocol deviations. Criteria for exclusion from the PP Analysis Set will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis population for efficacy analysis.

CCI [redacted]

10.2.2. Subject Disposition

The number of subjects enrolled, treated, prematurely discontinued from study drug (defined as those who discontinued study drug due to any reason except for PD) and those with major protocol deviations will be counted. The primary reason for study drug discontinued 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.

10.2.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the modified Safety Analysis Set using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cHL diagnosis, number of prior line of therapy for cHL; categorical variables include gender, ECOG, systemic symptoms (B symptoms), International Prognostic Score (IPS) at diagnosis, bulky disease defined as mediastinal mass ratio (MMR) of 0.33 or size of any single node/nodal mass is $\geq$ 10 cm in diameter, and ESR.

10.2.4. 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 (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. 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 subject's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

10.2.5. Efficacy Analyses

10.2.5.1. Primary Efficacy Analysis

In relapsed or refractory HL, ORR with single agent treatment as historical control is assumed to be approximately 35% based on historical trials. The ORR of tislelizumab in this study is assumed as 55%, which is deemed a clinically meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

$$H_0: \text{ ORR} = 35\%$$

$$H_a: \text{ ORR} > 35\%$$

A binomial exact test will be performed for hypothesis testing in the modified Safety Analysis Set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the single agent tislelizumab statistically significantly increases ORR compared with historical controls. Therefore, the superiority of single agent tislelizumab will be demonstrated.

A two-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the rate estimate.

Best Overall Response (BOR) is defined as the best response recorded from the first dose of tislelizumab until data cut or start of new anti-neoplastic treatment. Subjects with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories will be presented.

The primary efficacy analysis will be conducted approximately 8 months after the first dose of the last subject, and will be based on the modified Safety Analysis Set. The IRC assessment per the Lugano Classification (Cheson et al, 2014) will be used in the primary efficacy analysis.

10.2.5.2. Secondary Efficacy Analysis

The distribution of progression-free survival (PFS) will be estimated using the Kaplan-Meier method in the modified Safety Analysis Set. Progression-free survival at selected time points will be estimated with its 95% CI using Greenwood's formula. Progression-free survival censoring rule will follow the US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

Other time to event variables (e.g. DOR), will be analyzed similarly as PFS. TTR will be analyzed using sample statistics such as mean, median and standard deviation. Only subjects who have achieved an objective response will be included in the analysis of DOR and TTR.

Complete Response (CR) rate will be summarized in the modified Safety Analysis Set. Its Clopper-Pearson 95% CI will be calculated. The IRC assessment per the Lugano Classification (Cheson et al, 2014) will be used in the secondary efficacy analysis.

10.2.5.3. [redacted]

10.2.6. Safety Analysis

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (e.g. hematology, clinical chemistry, urinalysis), vital signs, and PEs, will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

10.2.6.1. Extent of Exposure

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

The number (percentage) of subjects 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.

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

10.2.6.2. 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 (Version 20.0 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (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 subject starts a new anti-cancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by System Organ Class (SOC) and Preferred Term. A subject will be counted only once by the highest severity grade per NCI-CTCAE v.4.03 within an SOC and Preferred Term, even if the

subject experienced more than 1 TEAE within a specific SOC and Preferred Term. The number (percentage) of subjects 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, related TEAEs and TEAEs that led to treatment discontinuation or dose interruption will be summarized.

10.2.6.3. Laboratory Analyses

Clinical laboratory (e.g. hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report (CSR) for this protocol. Descriptive summary statistics (e.g. 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 postbaseline visit.

Laboratory parameters that are graded in CTCAE v.4.03 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 (e.g. calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

10.2.6.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], heart rate, respiratory rate, temperature, weight, pulse oximetry) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by subject and visit.

10.2.7. CCI

[redacted]

10.2.8. CCI

[redacted]

10.3. Sample Size Consideration

The sample size calculation is based on the power of the comparison to the historical control rate, and assumed an ORR of 55% in the study as compared to 35% in the historical control. Using a binomial exact test, the power is 0.912 with 68 subjects in the modified Safety Analysis Set to demonstrate statistical significance at a 1-sided alpha of 0.025. The 95% exact CI would be (0.425, 0.671) with a sample size of 68 subjects, when the observed ORR is 0.55.

10.4. Interim Analysis

No interim analysis is planned for this study.

11. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1. 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.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" ICH guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

Investigators and all sub-investigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any sub-investigator. The Investigator and sub-investigator(s) agree to notify BeiGene of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol defined activities.

11.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted in accordance with GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki.

The Investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential subjects (e.g. advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The Investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the Investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before a new subject consents to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and

the approved amended informed consent form/other information must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

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 Investigator must utilize an IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

11.2.4. Investigator Reporting Requirements

The Investigator (or Sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, and an identification code (i.e. not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, CRFs, 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.

11.2.6. Case Report Forms

For each subject enrolled, a CRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time frame after data collection. This also applies to records for those subjects who fail to complete the study (even during a pre-randomization screening period if a CRF was initiated). If a subject withdraws from the study, the reason must be noted on the CRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.2.7. Drug Accountability

The Investigator or designee (i.e. 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), subject dispensing records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, subject initials, 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 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.

11.2.8. Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.3. Sponsor Responsibilities

11.3.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by BeiGene. All protocol modifications must be submitted to the IRB/IEC in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.3.2. Study Report and Publications

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.

For multi-center studies, the first publication or disclosure of study results shall be a complete, joint multi-center publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s).

After conclusion of the study and without prior written approval from BeiGene, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include BeiGene's CCI information.

The Investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with BeiGene's request to delete references to its CCI information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

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

11.4. 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.
- Return of treatment codes to the sponsor.
- CCI .

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. 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 it 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 IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned 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.

11.5. Records Retention and Study Files

11.5.1. Study Files and Retention of Records

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) subject clinical source documents.

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

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: subject 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 (e.g., 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 (e.g. 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 back up 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, transfer of ownership of 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 BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, 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.

11.6. Provision of Study Results and Information to Investigators

When the clinical study report (CSR) is completed, the Sponsor will provide the major findings of the study to the investigator.

In addition, details of the study drug assignment will be provided to the Investigator to enable him/her to review the data to determine the outcome of the study for his/her subject(s).

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

11.7. Information Disclosure and Inventions

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) is the sole property of the Sponsor.

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 are the sole property of the Sponsor, and are hereby assigned to the Sponsor.

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

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a subject'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.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.
- Information which is necessary to disclose in order to provide appropriate medical care to a subject.
- Study results which 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.

11.8. Joint Investigator/Sponsor Responsibilities

11.8.1. Access to Information for Monitoring

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

The monitor is responsible for routine review of the CRFs 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 subject records needed to verify the entries on the CRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

11.8.2. Access to Information for Auditing or Inspections

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

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13. APPENDICES

APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Single Arm, Multi-Center, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma

PROTOCOL NO: BGB-A317-203

This protocol is a CCI communication of BeiGene (Shanghai) Co., Ltd. I confirm that I have read this protocol, I understand it, and I will work in accordance with this protocol. 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 (Shanghai) Co., Ltd.

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: _____

_____

_____

_____

APPENDIX 2. CLINICAL LABORATORY ASSESSMENT

Serum Chemistry	CBC with Differential	Coagulation	Urinalysis
Sodium	RBC	PT	pH
Potassium	Hematocrit	aPTT	Specific gravity
Chloride	Hemoglobin	INR	Glucose
Bicarbonate	MCH		Protein
BUN	MCHC		Ketones
Creatinine	MCV		Blood
LDH	RDW		
Glucose	Platelet		
Calcium	WBC with differential		
AST (SGOT)	Neutrophil		
ALT (SGPT)	Lymphocyte		
Total bilirubin	Monocyte		
Conjugated bilirubin	Eosinophil		
Alkaline phosphatase	Basophil		
Total protein			
Magnesium			
Phosphorus			
Uric acid			
Albumin			
Creatine kinase (CK)			
Creatine kinase-cardiac muscle isoenzyme (CK-MB)*			

AST: aspartate aminotransferase; ALT: alanine aminotransferase; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; RDW: red cell distribution width; WBC: white blood cell count; RBC: red blood cell count; PT: prothrombin time; aPTT: activated partial thromboplastin time; INR: international normalized ratio; LDH: lactate dehydrogenase; BUN: blood urea nitrogen; pH: pouvoir hydrogene
* In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

APPENDIX 3. HODGKIN LYMPHOMA STAGING

Stage	Involvement
I	Involvement of a single lymph node region (I) or localized involvement of a single extra-lymphatic organ or site (I_E)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extra-lymphatic organ or site and its regional lymph node(s), with or without involvement of other lymph node regions on the same side of the diaphragm (II_E)
III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of an associated extra-lymphatic organ or site (III_E), or by involvement of the spleen (III_S), or by both (III_{E+S})
IV	Disseminated (multifocal) involvement of one or more extra-lymphatic organs, with or without associated lymph node involvement, or isolated extra-lymphatic organ involvement with distant (non-regional) nodal involvement

A: No systemic symptoms present
B: Unexplained fevers > 38°C; drenching night sweats; or weight loss > 10% of body weight within 6 months prior to diagnosis

APPENDIX 4. INTERNATIONAL PROGNOSTIC SCORE

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

APPENDIX 5. SCHEDULE OF ASSESSMENT

	Screening [1]	Treatment Period			Safety Follow-up[2]	Safety/Survival/Efficacy Follow-up[3]
		Cycle 1 (21 Days) [22]	Cycle 2 and additional cycles (every 21 days)	EOT [19]		
Days	**-28 to -1**	**1 ± 3**	**1 ± 3**		**30 ± 7 (after last dose)**	
Informed consent [4]	x					
Inclusion/exclusion criteria	x					
Demographic/Medical history/ Prior medications [5]	x					
Vital signs [8]	x	x	x	x	x	
Height and weight [21]		x	x	x		
Physical examination	x	x	x	x	x	
ECOG performance status	x	x	x	x	x	
12-lead ECG [10]	x				x	
Pulmonary function test	x					
Review adverse events [9]	x	x	x	x	x	x
Review concomitant medications [12]	x	x	x	x	x	x
CBC with differential [13]	x	x	X[25]	x	x	

	Screening [1]	Treatment Period			Safety Follow-up[2]	Safety/Survival/Efficacy Follow-up[3]
		Cycle 1 (21 Days) [22]	Cycle 2 and additional cycles (every 21 days)	EOT [19]		
Days	**-28 to -1**	**1 ± 3**	**1 ± 3**		**30 ± 7 (after last dose)**	
Serum chemistry panel [13]	x	x	X[25]	x	x	
Coagulation parameters [14]	x					
Hepatitis B and C and HIV[15]	x					
ESR		X[25]				
Urinalysis		X[25]	x[25] (Start at C7D1, repeat every 6 cycles)	x	x	
Pregnancy test [17]	x			x		
Thyroid function test [16]		X[25]	X[25] (after C2/D1, repeat every 2 cycles)	x	x	
Tumor tissue [6]	x					
Tumor imaging [7,20]	x	Week 12, Week 18, then every 12 weeks in the first year, and every 15 weeks thereafter, ± 7 days		x [20]		x[20]
ECHO or MUGA [11]	x					

	Screening [1]	Treatment Period			Safety Follow-up[2]	Safety/Survival/Efficacy Follow-up[3]
		Cycle 1 (21 Days) [22]	Cycle 2 and additional cycles (every 21 days)	EOT [19]		
Days	**-28 to -1**	**1 ± 3**	**1 ± 3**		**30 ± 7 (after last dose)**	
Bone marrow aspirate/biopsy [23]	x					
CCI						C
Study drug administration[26]		x	x			
C						
Anti-drug antibody [24]		x	x		x	

Abbreviations: AE, adverse event; aPTT, activated partial thromboplastin time; C, cycle; CBC, complete blood count; cHL, classical Hodgkin lymphoma; CR, complete response; CRF, case report form; CT, computed tomography; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; 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; ICF, informed consent form; INR, international normalized ratio; 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; CCI ; PT, prothrombin time; SAE, serious adverse event; TSH, thyroid stimulating hormone.

1. All assessments mandated throughout the study must be performed on a calendar schedule. Screening procedures may be performed up to 28 days prior to first dose of treatment. Screening procedures that have a different visit window are indicated in parentheses.
2. The mandatory Safety Follow-up Visit should be conducted after initiation of study drug, and all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after last dose of study treatment. Subjects 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 subject is lost to follow up, whichever comes first.
3. CCI

4. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe (e.g. within 28 days prior to Cycle 1 Day 1). Assign baseline number when the study informed consent is signed.
5. 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. Radiographic studies performed prior to study entry may be collected for review by the Investigator. Report complete medication history for 28 days prior to the Screening Visit (Visit 1).
6. CCI [redacted]
7. Tumor imaging (CT with contrast of neck, chest, abdomen and pelvis, and PET/CT) 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 main study ICF, 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, Week 12, Week 18, then every 12 weeks in the first year, and every 15 weeks thereafter (± 7 days), 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 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. PET/CT can be performed in lieu of a CT with contrast only if the CT is performed with diagnostic quality and contrast is administered. Total body MRI may be substituted for CT if CT with contrast is contraindicated. PET/CT should be performed, in addition to during Screening Period, at Weeks 12, 24, 42, 57, and every 30 weeks thereafter. PET/CT should also be performed at PD suspected clinically or by CT, and CR suspected clinically or by CT.
8. Vital signs to include temperature, blood pressure, pulse, respiratory rate, and pulse oximetry.
9. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE version 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
10. At each time point listed, a single 12-lead ECG will be performed by qualified site personnel after the subject 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 subject'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.
11. Echocardiography (ECHO) or Multigated Acquisition Scan (MUGA) is required at Screening unless performed within 90 days of first day of Screening (Visit 1).
12. All Concomitant Medications within 28 days prior to first study treatment and until 30 days after the last dose of study treatment should be recorded in the CRFs. Any new anti-cancer therapy, if taken after treatment discontinuation, will also be recorded.
13. 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. Re-screening 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.
14. Coagulation parameters (PT, INR, aPTT) should be determined at Screening and during study treatment as clinically indicated.
15. Testing will be performed at Screening and includes Hepatitis C virus (HCV) antibody, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb), and HIV testing. Subjects 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 5 for additional information).
16. TSH, free T4, and free T3 will be performed.

17. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 72 hours before the first investigational product administration). Subsequent tests may be urine tests, and should be performed as clinically indicated.
18. CCI [redacted]
19. When subjects go off treatment, they will need to undergo EOT visit within 7 days of last dose of tislelizumab.
20. Tumor imaging for EOT does not have to be performed if the most recent tumor imaging was performed within the previous 6 weeks. For subjects who discontinue study treatment for reason other than PD, tumor imaging will be performed every 12 weeks (± 7 days) until PD, new anti-cancer therapy, withdrawal of consent, death, lost to follow-up, or EOS, whichever occurs first.
21. Height only needs to be measured on Day 1 of Cycle 1.
22. 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 and re-testing on Day 1 of Cycle 1 is not required.
23. CCI [redacted]
24. CCI [redacted]
25. These tests should be completed within 3 days before the start of next cycle.
26. Subjects still receiving study treatment when the roll-over study is open will transfer to roll-over study for continuous treatment.

APPENDIX 6. THE LUGANO CLASSIFICATION

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following): Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extra-lymphatic sites of disease
Lymph nodes and extra-lymphatic sites	Score 1, 2, 3* with or without a residual mass on 5PS[†] It is recognized that in Waldeyer's ring or extra-nodal sites with physiologic uptake or with activation within spleen or marrow (e.g., 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	
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	Partial metabolic response	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
Lymph nodes and extra-lymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	
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

Response and Site	PET-CT-Based Response	CT-Based Response
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
No response or stable disease	No metabolic response	Stable disease < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extra-nodal sites; no criteria for progressive disease are met
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	
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

Response and Site	PET-CT-Based Response	CT-Based Response
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following 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 (e.g. 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
Individual target nodes/nodal masses	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	
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Response and Site	PET-CT-Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., 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

Cheson BD, Fisher RJ, Barrington SF, et al. J Clin Oncol 2014;32(27):3059-67.

Abbreviations: PET, Positron Emission Tomography; CCI; PS, point scale; PPD, purified protein derivative; LD, longest diameter; SD, shortest diameter; CT, Computed Tomography; FDG, fluorodeoxyglucose.

*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). 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 (e.g. 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 (e.g., 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 (e.g., 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 7. CCI

APPENDIX 8. 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 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 *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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

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 patients experience 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.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency

virus; INR, international normalized ratio; LCI, liver cystolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-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])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms		Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/ Diarrhea	**1** Mild symptoms: < 3 liquid stool 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 1-2mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: • For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. • For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

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.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: • If on oral prednisolone change to pulsed IV methylprednisolone • If on IV add mycophenolate mofetil (MMF) 500-1000 mg twice a day • If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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 > 1.5-3X baseline or > 1.5-3X 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 > 3-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection	Discontinue study treatment.
Myositis/ **Rhabdomyolysis**	1 Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Myocarditis	< 2 Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	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	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

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