CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Phase 2, Open-Label Study of BGB-A317 in Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms
Protocol Identifier:	BGB-A317-207
Phase:	2
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Relapsed or Refractory Mature T- and NK-cell Neoplasms
EudraCT:	2017-003700-44
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
Sponsor Medical Monitor:	[redacted] Phone number: [redacted] Email: [redacted]
Original Protocol:	01 September 2017
Amendment 1.0	15 December 2017
Amendment 2.0	23 August 2018
Amendment 3.0	14 March 2019

FINAL PROTOCOL APPROVAL SHEET

Study BGB-A317-207: A Phase 2, Open-Label Study of BGB-A317 in Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms

BeiGene, Ltd. Approval:

_____ _____

[redacted] Date

[redacted]

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Tislelizumab (BGB-A317)

Title of Study: A Phase 2, Open-Label Study of BGB-A317 in Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms

Protocol Identifier: BGB-A317-207

Phase of Development: 2

Number of Patients: Up to 130, divided into three cohorts

Study Centers: Approximately 35 centers internationally

Study Objectives:

Primary:

To evaluate efficacy, as measured by overall response rate and determined by investigator.

- For cohorts 1 and 2, overall response rate will be measured using the Lugano criteria (Cheson et al 2014) with the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification for immunomodulatory drugs (Cheson et al 2016).
- For cohort 3, overall response rate will be measured using the International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) guidelines (Olsen et al 2011).

Secondary:

For cohorts 1 and 2, efficacy measures will be determined using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016). For cohort 3, efficacy measures will be determined using the ISCL/EORTC guidelines (Olsen et al 2011).

- To evaluate efficacy, as measured by the following and determined by investigator:
  - Duration of response for all cohorts
  - Progression-free survival for all cohorts
  - Overall survival for cohorts 1 and 2
  - Rate of complete response or complete metabolic response for all cohorts
  - Time to response for all cohorts
  - Patient-reported outcomes (EQ-5D-5L and EORTC QLQ-C30) for all cohorts
- To evaluate the safety and tolerability of tislelizumab for all cohorts

Exploratory:

- [redacted]

Study Design:

This is a multicenter, prospective, non-randomized, open-label, phase 2 clinical study to evaluate the safety and efficacy of tislelizumab in patients with relapsed or refractory mature T- and natural killer (NK)-cell neoplasms. There will be three cohorts of patients:

- Cohort 1: patients with relapsed or refractory extranodal NK/T-cell lymphoma (nasal or non-nasal type); patients with aggressive NK leukemia are excluded
- Cohort 2: patients with relapsed or refractory mature T-cell neoplasms limited to the following

histologies: peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma, and anaplastic large-cell lymphoma
- Cohort 3: patients with relapsed or refractory cutaneous T-cell lymphomas, limited to mycosis fungoides or Sèzary syndrome, stage IB or higher

Up to 70 patients will be enrolled into cohort 1, up to 50 patients into cohort 2, and up to 10 patients into cohort 3 for a total sample size of up to 130 patients. Cohort 2 will include up to 20 patients with peripheral T-cell lymphoma-not otherwise specified; up to 10 patients with angioimmunoblastic T-cell lymphoma; and up to 20 patients with anaplastic large-cell lymphoma. Cohort 3 will be available for accrual only in North America (US and Canada) and in the EU (Italy, France, and Germany).

EBV status will be determined by EBV-encoded RNAs (EBER) in situ hybridization (ISH) from local pathology report or, if not available, from testing on archival or fresh tumor tissue. The primary efficacy endpoint is overall response rate (ORR) determined by investigator assessment. Disease response for the primary endpoint for cohorts 1 and 2 will be assessed per the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory therapy (Cheson et al 2016). Disease response for the primary endpoint for cohort 3 will be assessed per the ISCL/EORTC guidelines (Olsen et al 2011). Study treatment must commence within 5 days after screening assessments have been completed and study eligibility has been determined. Each cycle consists of 21 days.

Study Assessments:

Assessments of lymphoma status during the study include: disease-related constitutional symptoms; physical examination of lymph nodes, liver, spleen, and skin; complete blood count (CBC); circulating EBV DNA (if EBV-positive by EBER ISH at screening); bone marrow examination (core biopsy); imaging studies including positron emission tomography (PET)-computed tomography (CT) and CT-based assessments; peripheral blood flow cytometry (for cohort 3 patients only); and patient-reported outcomes (PRO).

For cohorts 1 and 2, screening findings will determine whether patients are followed with PET-CT-based or CT-based assessments on study. That is, patients whose disease is not PET-avid will be followed by CT-based assessments alone while patients whose disease is PET-avid will be followed by an integration of PET-CT and CT-based assessments (as described in Section 5.4.1 and in Appendix 11). Tumor assessments, including imaging studies, will be performed at screening, at Week 12 starting from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. Patients in cohort 2 whose disease is EBV-negative by EBER ISH at screening are not required to undergo subsequent EBV DNA assessments during screening and study treatment periods.

For cohort 3, since not all patients have disease that is measurable by CT scan, patients will be followed by ISCL/EORTC response criteria (Olsen et al 2011), which includes composite assessments of skin by modified severity weight assessment tool (mSWAT), as described in Appendix 14, lymph nodes and visceral disease assessed by PET and/or CT, and blood tumor burden of circulating Sèzary cells (CSC) by flow cytometry . Assessments will be performed starting at Week 12 from Cycle 1 Day 1, then every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. Patients who are suspected to have progression at Week 12 will have a confirmatory response assessment at Week 16 using the same assessment(s) that indicated progression (eg, if mSWAT but not CT scan indicates progression at Week 12, then only mSWAT is required at Week 16).

CT-based assessments should be of diagnostic quality with contrast administered. Patients with PET-avid disease in cohorts 1 and 2 and patients with nodal disease in cohort 3 undergoing a tumor assessment at a timepoint when PET-CT is required should ideally undergo a diagnostic quality, contrast-enhanced CT during a single visit combined with PET. If that is not possible, then a

diagnostic quality, contrast-enhanced CT can be done as a separate study from PET-CT. Magnetic resonance imaging (MRI) may be substituted for diagnostic quality, contrast-enhanced CT for patients with serious contrast allergy. Assessment of tumor response will be made by the investigator.

All patients should remain on study treatment until disease progression is confirmed by the investigator. Patients have the right to voluntarily withdraw from the study and the investigator has the right to discontinue a patient from study treatment at any time, including for a medical condition that may jeopardize the patient's safety.

Patients assessed as having a complete response (CR) and who had bone marrow involvement at screening will have a bone marrow examination to confirm the CR.

Assessments of safety will include adverse events (AEs), serious AEs (SAEs), clinical laboratory tests, physical examinations, pulmonary and cardiac function tests, electrocardiograms, Eastern Cooperative Oncology Group (ECOG) performance status, ophthalmologic examinations, and vital signs. AEs will be graded for severity per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. An independent data monitoring committee will periodically monitor safety data.

Key Eligibility Summary and Patient Selection:

The patients to be included in this trial will have a histologically confirmed diagnosis of mature T-cell and NK-cell neoplasms (or lymphoma) based on the World Health Organization (WHO) 2016 classification of tumors of hematopoietic and lymphoid tissue, and the presence of measurable disease by the Lugano criteria for cohorts 1 and 2 and by ISCL/EORTC criteria for cohort 3. Either unstained tissue (block or unstained slides) or stained slides or fresh tissue are acceptable to be sent together with a pathology report to the central laboratory for pathology confirmation of mature T-cell or NK-cell lymphoma diagnosis. Patients will be allocated to one of three cohorts based on their histologic diagnosis:

- Cohort 1: relapsed or refractory extranodal NK/T cell-lymphoma (nasal or non-nasal type)
- Cohort 2: other mature T-cell neoplasms (limited to the following histologies: peripheral T-cell lymphoma-not otherwise specified, angioimmunoblastic T-cell lymphoma, or anaplastic large-cell lymphoma)
- Cohort 3: cutaneous T-cell lymphoma (limited to mycosis fungoides and Sèzary syndrome)

Patients must have previously received appropriate first-line systemic therapy (eg, non-anthracycline-based regimen such as L-asparaginase-based therapy for patients in cohort 1 or combination chemotherapy for patients in cohort 2) and had disease progression during or after completion of most recent therapy or refractory disease. Patients will have adequate organ function, will not have active autoimmune disease and will have no active infection with hepatitis B or C, HIV, or human T-cell lymphotropic virus.

Test Product, Dose, and Mode of Administration:

Tislelizumab 200 mg administered intravenously every three weeks. A cycle is 3 weeks (21 days) in length.

Statistical Methods:

The Primary analysis set for both efficacy and safety analyses will be the Safety analysis set (all patients who received at least one dose of study medication). All efficacy analyses will be performed by cohort; all safety analyses will be performed by cohort and combined. For cohorts 2 and 3, additional efficacy analyses by subtype will be conducted.

Primary Efficacy Endpoint Analysis:

The primary efficacy endpoint for cohorts 1 and 2 is ORR according to the Lugano criteria (Cheson et al 2014) with the LYRIC modification for immunomodulatory therapy (Cheson et al 2016) as assessed by the investigator. The primary efficacy endpoint for cohort 3 is ORR according to ISCL/EORTC response criteria (Olsen et al 2011) as assessed by the investigator. Efficacy will be assessed every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly

until disease progression. ORR is defined as the proportion of patients achieving a best overall response of CR or partial response (PR). Two-sided Clopper-Pearson 95% confidence interval (CI) for ORR will be calculated.

Patients with no post-baseline response assessment will be considered non-responders for the purposes of analysis. The proportion for each response category (CR, PR, stable disease [SD], and progressive disease) will be presented. The primary efficacy analysis for each cohort will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient in each cohort has received the first dose of study drug.

Secondary Efficacy Endpoint Analyses:

PFS and overall survival (OS) will be analyzed by Kaplan-Meier method. Median and other quartiles will be estimated along with their 2-sided 95% CIs using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for PFS and OS will be estimated with their CIs using the Greenwood formula. Duration of response will be analyzed using the same methods as PFS and OS, but only for patients who have achieved an objective response. Complete response rate will be analyzed using the same methods applied for ORR analysis. Time to response will be summarized only for responders by sample statistics such as mean, median, range, and standard deviation. Secondary efficacy measures will be presented as assessed by the Lugano criteria (Cheson et al 2014) with the LYRIC modification for immunomodulatory therapy (Cheson et al 2016) for cohorts 1 and 2 and as assessed by ISCL/EORTC response criteria (Olsen et al 2011) for cohort 3. The EORTC QLQ-C30 and EQ-5D-5L questionnaires will be utilized for all cohorts. The scores and their changes from baseline will be summarized.

Safety, Pharmacokinetic, and Immunogenicity Analyses:

The Safety analysis set (all patients who received at least one dose of study medication) will be used for all safety analyses. Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (eg, hematology, clinical chemistry), vital signs, pulmonary and cardiac function tests, electrocardiograms, ECOG performance status, ophthalmologic examinations, and physical examinations will also be used in determining safety. Drug exposure will be summarized by duration, dosage, and dose intensity.

Tislelizumab postdose and trough serum concentration data (C_{trough}) will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate. Additional pharmacokinetic (PK) analyses will be conducted as appropriate.

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

Sample Size Considerations:

The sample size is based on the precision of the estimates of the ORR. With 10, 20, 50 and 70 subjects in each cohort/subtype, if the observed ORR is 30%, the corresponding exact 95% CIs are as follows: 10 subjects (6.67%, 65.25%); 20 subjects (11.89%, 54.28%); 50 subjects (17.86%, 44.61%); and 70 subjects (19.62%, 42.13%).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large-cell lymphoma
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BGB-A317	tislelizumab
CAR-T	Chimeric antigen receptor T cell
CBC	complete blood count
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase - cardiac muscle isoenzyme
CR	complete response
CRS	cytokine release syndrome
CSC	circulating Sèzary cell
CT	computed tomography
EBER	Epstein Barr virus encoded RNAs
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FcγR	gamma Fc receptor (eg, Fcγ-RI, Fcγ-R2I)
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FVC	forced vital capacity
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational New Drug
IR	indeterminate response
irAE	immune-related adverse event
IRB	Institutional Review Board
ISH	in situ hybridization

Abbreviation	Definition
ISCL/EORTC	International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer
LYRIC	lymphoma response to immunomodulatory therapy criteria
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MRI	magnetic resonance imaging
mSWAT	modified severity weight assessment tool
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	natural killer (cell)
NOS	not otherwise specified
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PTCL-NOS	peripheral T-cell lymphoma-not otherwise specified
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
SS	Sèzary syndrome
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
v	version

1. INTRODUCTION

1.1. Mature T- and NK-cell Neoplasms

Mature T-cell and natural killer (NK)-cell lymphomas are lymphoid malignancies that are derived from T-cell and NK-cell lineages. They are less prevalent than B-cell lymphomas. Interestingly, there are distinct geographic differences in their distribution and prevalence. Nodal lymphomas including peripheral T-cell lymphoma - not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and cutaneous T-cell lymphomas are more common in Western populations, accounting for about 10% of all lymphomas. In Asian countries, however, mature NK- and T-cell lymphoma, nasal type, is much more prevalent, constituting as many as 25% of all lymphomas, with AITL, ALCL, and PTCL-NOS accounting for another 10%. Epstein Barr virus (EBV) infection is found in almost all cases of extranodal NK/T-cell lymphomas, the majority of angioimmunoblastic T-cell lymphoma, and a significant proportion of PTCL-NOS, implying that it plays an important pathogenetic role.

1.1.1. Treatment Options for Mature T- and NK-cell Neoplasms

Conventional chemotherapeutic regimens designed for aggressive B-cell lymphomas are generally less effective when applied to mature T-cell and NK-cell lymphomas. The treatment outcome for relapsed or refractory disease is especially poor. In a recent retrospective analysis, the median overall survival (OS) and progression-free survival (PFS) in patients with disease relapse were found to be only 5.5 and 3.1 months, respectively (Mak et al 2013). The efficacy of newly approved agents such as pralatrexate and romidepsin for relapsed or refractory T-cell lymphomas is modest, with an average overall response rate (ORR) of around 20-30% only (Coiffier et al 2014). Novel therapeutic approaches are therefore needed for this group of patients with dismal prognosis.

1.2. Cutaneous T-Cell Lymphomas

Cutaneous T-cell lymphomas (CTCL) are mature T-cell non-Hodgkin lymphomas that manifest primarily in the skin, leading to symptoms such as pruritis, erythema, and the formation of patches or plaques. Mycosis fungoides (MF) and Sèzary syndrome (SS) are the most common variants of CTCLs (Hoppe et al 1995). While MF is commonly limited to the skin and has an indolent course, SS is considered more aggressive, with leukemic phase and wide involvement of visceral organs (Horwitz et al 2008). Patients with MF may experience accelerated progression in association with large cell transformation or involvement of the hair follicles by malignant T cells.

1.2.1. Treatment Options for Cutaneous T-Cell Lymphomas

CTCLs are largely incurable; treatment is therefore directed towards extended periods free of progression. Because of the location of disease, patients with early-stage MF (stage IA, IB, IIA) are typically treated with skin-directed therapies, including topical corticosteroids, topical cytotoxic chemotherapies, retinoids, phototherapy, or radiation (NCCN Guidelines Version 2.2019). Advanced disease (stage IIB or higher) is typically treated with systemic therapies. Current US Food and Drug Administration (FDA)-approved therapies for MF and SS include denileukin difitox (Olsen et al 2001), bexarotene (Duvic et al 2001), vorinostat (Olsen et al 2007), and romidepsin (Whittaker et al 2010). Unfortunately, response rates for these agents are between 30-40%, with duration of responses between 6-12 months. Given these modest response rates and duration of responses, novel approaches to treatment of these patients are needed.

1.2.1.1. Anti-PD-1/Anti-PD-L1 Therapy for Mature T- and NK-cell Neoplasms

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

PD-1 expression is markedly upregulated in tumor-infiltrating lymphocytes, 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 (eg, interferon-α and interferon-γ) in the tumor microenvironment. Furthermore, increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor cells and tumor-associated stromal cells have been observed in many types of solid tumors (Jin and Yoon 2016; Ono Pharmaceutical Co 2017; Patel and Kurzrock 2015; Van Der Kraak et al 2016; McDaniel et al 2016; Gong et al 2011).

These data provide a basis for the use of PD-1 antagonists as immuno-oncologic agents. The therapeutic approach of blocking PD-1 and PD-L1 interactions has recently demonstrated efficacy in a variety of tumor types. Monoclonal antibodies to PD-1, such as nivolumab and pembrolizumab, have the ability to bind to PD-1, thus disrupting interactions between the protein and its ligands (PD-L1 and PD-L2) and impeding inhibitory signals in the T-cell microenvironment (Wang et al 2014). These monoclonal antibodies have now been approved for the treatment of several cancers, including bladder, lung, head, and neck squamous cell carcinomas, as well as melanoma, in the US, Europe, and beyond.

PD-1 blockade using anti-PD-1 monoclonal antibody (mAb) has been shown effective for relapsed/refractory classical Hodgkin lymphoma. Furthermore, clinical response has also been seen in relapsed T-cell lymphomas after treatment with anti-PD-1 antibody in phase 1 studies (Lesokhin et al 2016). In addition, previous reports have shown that EBV infection may enhance the expression of PD-L1 in tumor cells, and that some EBV-associated lymphomas such as mature T-cell and NK-cell lymphoma express high level of PD-L1, suggesting that EBV-associated mature T-cell and NK-cell lymphomas may be more susceptible to PD-1 blockade (Wilcox et al 2009; Chen et al 2013; Jo et al 2017). A recent study showed that PD-1 blockade with low-dose pembrolizumab resulted in positive outcomes for patients with mature T-cell and NK-cell lymphomas who had previously failed L-asparaginase regimens (Kwong et al 2017).

PD-1 blockade may also be effective in relapsed/refractory CTCLs. PD-1 and PD-L1 expression is seen on malignant T cells from MF and SS patients (Kantekure et al 2012; Samimi et al 2010). Data from a phase 1 study of nivolumab in hematologic malignancies in 13 patients with MF showed 2 patients with partial response (PR) and 9 patients with stable disease (SD) (Lesokhin et al 2016). The activity of pembrolizumab in relapsed/refractory MF and SS was assessed in the recently completed CITN-10 study (Khodadoust et al 2016; Khodadoust et al 2018; Dai et al 2018). The primary endpoint in this study was investigator-assessed ORR utilizing Olsen global assessments. Secondary endpoints included PFS, safety, duration of response, and time to response. For the 24 patients enrolled, ORR was 38%. Of the 9 patients enrolled with MF, 5 patients experienced PR, 2 experienced SD, and 2 patients had progressive disease. Of the 15 patients enrolled with SS, 2 patients experienced CR, 2 experienced PR, 7 patients had SD, and 4 patients experienced progressive disease. Notably, 8 of 15 patients with SS experienced a tumor skin flare, as evidenced by increases in erythroderma and pruritis. Patients with a tumor skin flare had a substantial increase in modified severity weight assessment tool (mSWAT) score at the first assessment, followed by a significant decrease afterwards. Therefore, patients with a skin flare, while normally meeting criteria for progression, were maintained on treatment and often had resolution of the flare within 4 weeks in a phenomenon that mirrors pseudoprogression (see Section 5.4.4).

1.2.1.2. 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 2012). Median time to onset of treatment-related adverse events (AEs) 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 CIs 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 is a humanized, IgG4-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

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

The IgG4-variant antibody has very low binding affinity to FcγRIIIA and complement 1q, a subunit of complement 1, by *in vitro* assays, suggesting either low or no antibody-dependent cellular toxicity or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009).

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

Tislelizumab was manufactured under Good Manufacturing Practice quality control systems. The clinical trial drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolality. The suggested administration route is intravenous infusion after the appropriate dilution in 0.9% sodium chloride solution.

1.3.1. Summary of Clinical Pharmacology

1.3.1.1. Pharmacokinetics Results

An interim pharmacokinetic (PK) analysis (data cutoff date of 08 October 2016) was conducted by noncompartmental analysis methods, using serum concentrations from patients who received doses of tislelizumab 0.5, 2.0, 5.0, and 10 mg/kg every 2 weeks and patients who received doses of 2.0 and 5.0 mg/kg every 3 weeks in Study BGB-A317_Study_001 (phase 1a, part 1 and part 2). The C_{max} and drug exposure (ie, 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.

Population PK analysis was conducted 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 terminal elimination half-life ($t_{1/2}$) was approximately 17 days.

Patients' body weight is not a significant covariate on the clearance of BGB-A317, which supports fixed dosing.

1.3.1.1.1. Lack of Ethnic Differences in Exposure

Based on the information available to date, tislelizumab exposure in Asian and Caucasian patients is similar, and the safety profile at clinically relevant doses is tolerable and manageable.

Preliminary PK data from Study BGB-A317_Study_001 are summarized in Section 1.3.1.1. Comparison of PK parameters indicates that after a single intravenous infusion of tislelizumab, dose-normalized exposure was consistent across Asian (n=10) and Caucasian (n=93) patients in the study, which was conducted in the US, Australia, New Zealand, Korea, and Taiwan. Additionally, dose-normalized exposure was consistent between Study BGB-A317_Study_001, in which most patients were Caucasian (n=107) and Study BGB-A317-102, conducted in Chinese patients (n=6).

These preliminary findings indicate that ethnic differences are unlikely to affect the exposure of tislelizumab.

Furthermore, these data are consistent with findings of limited ethnic differences in studies of therapeutic monoclonal antibodies (Chiba et al 2014). In addition, there do not appear to be clinically relevant differences in PK exposures from studies of 2 other anti-PD-1 antibodies, nivolumab (Yamamoto et al 2017) and pembrolizumab (Shimizu et al 2016).

1.3.2. Summary of Relevant Clinical Experience with BGB-A317

For details of the current, ongoing studies with tislelizumab, please refer to the most current tislelizumab Investigator's Brochure.

As of a 28 August 2017 data cutoff, 438 patients have received ≥ 1 dose of tislelizumab in the monotherapy study BGB-A317_Study _001, the most recent results of which are briefly summarized below.

1.3.2.1. Study BGB-A317_Study_001

Study BGB-A317_Study_001 is an ongoing two-stage study consisting of a dose escalation and dose-finding component to establish the maximum tolerated dose (Part 1), if any, and recommended phase 2 dose, followed by a dose expansion component (phase 1b) to investigate efficacy in select advanced solid tumor types and to further evaluate safety and tolerability of tislelizumab at the expansion cohort dose. Phase 1A, Part 3 was added to evaluate the safety and PK of tislelizumab at fixed dose (200 mg every 3 weeks) that did not exceed the exposure of the maximum tolerated dose as determined in the phase 1a, Part 1.

1.3.2.1.1. Safety Results (28 August 2017 data cutoff date)

Phase 1a Component:

As of a data cutoff of 28 August 2017, treatment-emergent adverse events (TEAEs) had been reported in 99.1% of patients across all 3 parts of the phase 1a component. The most frequently occurring TEAEs (≥ 20%) included fatigue (42.2%), nausea (33.6%), diarrhea (26.7%), constipation (22.4%) and abdominal pain (22.4%). There was no apparent correlation between dose level (2 mg/kg, 5 mg/kg, or 10 mg/kg) and either the incidence or the severity of TEAEs.

Forty-eight (48) of the 116 total patients (41.4%) experienced ≥ Grade 3 TEAEs. The most frequently reported ≥ Grade 3 TEAEs (≥ 2%) patients included abdominal pain (4.3%) and anaemia (4.3%), and the following were reported in 3 patients (2.6%): ascites, pneumonia, pleural effusion, pneumothorax,

pulmonary embolism, type I diabetes mellitus, fatigue, back pain, musculoskeletal chest pain, and hypertension.

Table 1 shows the most frequently occurring TEAEs (≥ 10%) in Study BGB-A317 Study _001, Phase 1a.

Table 1: Treatment-Emergent Adverse Events in ≥ 10% of Patients and Corresponding Incidence at ≥ Grade 3 Severity – Study BGB-A317_Study _001, Phase 1a

	Overall Incidence (All Severity Grades)	≥ Grade 3 Severity
MedDRA System Organ Class Preferred Term	**N = 116 n (%)**	**N = 116 n (%)**
Patients with ≥ 1 TEAE	**115 (99.1)**	**48 (41.4)**
Gastrointestinal disorders		
Nausea	39 (33.6)	2 (1.7)
Diarrhoea	31 (26.7)	1 (0.9)
Constipation	26 (22.4)	1 (0.9)
Vomiting	20 (17.2)	0
Abdominal pain	26 (22.4)	5 (4.3)
General disorders and administration site conditions		
Fatigue	49 (42.2)	3 (2.6)
Respiratory, thoracic and mediastinal disorders		
Cough	15 (12.9)	0
Dyspnoea	16 (13.8)	1 (0.9)
Musculoskeletal and connective tissue disorders		
Back pain	20 (17.2)	3 (2.6)
Skin and subcutaneous tissue disorders		
Rash	23 (19.8)	0
Pruritus	20 (17.2)	0
Infections and infestations		
Upper respiratory tract infection	12 (10.3)	0
Metabolism and nutrition disorders		
Decreased appetite	19 (16.4)	0
Blood and lymphatic system disorders		
Anaemia	12 (10.3)	5 (4.3)

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events.
Notes: Data as of 28 August 2017.
A treatment-emergent adverse event is defined as any AE that starts on or after the dosing date, or (in the case of a continuing AE) worsens in severity during treatment relative to the pre-treatment state.
All AEs are coded using MedDRA Version 19.0 or later and graded according to NCI-CTCAE v4.03.
Any patient with multiple occurrences of the same AE is counted only once in the AE category.

Phase 1b Component:

As of 28 August 2017, 322 patients have been enrolled in the Phase 1b component of protocol BGB-A317_Study_001. Also, as of the data cutoff, 301 of the 322 total patients (93.5%) in the phase 1b component of Study BGB-A317_Study _001 had at least 1 TEAE. The most frequently reported TEAEs (≥ 10%) included fatigue (20.5%), nausea (18.6%), decreased appetite (18.6%), diarrhea (13.0%), vomiting (12.7%), constipation (12.4%), abdominal pain (10.2%), cough (10.2%), and back pain (11.8%). One hundred fifty-four (154) of the 322 total patients (47.8%) experienced ≥ Grade 3 TEAEs. The most frequently reported ≥ Grade 3 events included pneumonia (4.0%), dysphagia (2.5%), anaemia (2.5%), pleural effusion (2.5%), vomiting (2.2%), hypokalaemia (2.2%), and AST increased (2.2%).

Table 2 shows the most frequently occurring TEAEs (≥ 10%) in Study BGB-A317_Study _001, Phase 1b.

Table 2: Treatment-Emergent Adverse Events in ≥ 10% of Patients and Corresponding Incidence at ≥ Grade 3 Severity – Study BGB-A317_Study _001, Phase 1b

	Overall Incidence (All Severity Grades)	**≥ Grade 3 Severity**
MedDRA System Organ Class Preferred Term	**N = 322** **n (%)**	**N = 322** **n (%)**
Patients with ≥ 1 TEAE	**301 (93.5)**	**154 (47.8)**
Gastrointestinal disorders		
Nausea	60 (18.6)	3 (0.9)
Diarrhoea	42 (13.0)	5 (1.6)
Vomiting	41 (12.7)	7 (2.2)
Constipation	40 (12.4)	2 (0.6)
Abdominal pain	33 (10.2)	4 (1.2)
General disorders and administration site conditions		
Fatigue	66 (20.5)	4 (1.2)
Respiratory, thoracic and mediastinal disorders		
Cough	33 (10.2)	0
Musculoskeletal and connective tissue disorders		
Back pain	38 (11.8)	3 (0.9)
Skin and subcutaneous tissue disorders		
Pruritus	24 (7.5)	0
Metabolism and nutrition disorders		
Decreased appetite	60 (18.6)	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute -Common Terminology Criteria for Adverse Events.
Notes: Data as of 28 August 2017.
A treatment-emergent adverse event is defined as any AE that starts on or after the dosing date, or (in the case of a continuing AE) worsens in severity during treatment relative to the pretreatment state.
All AEs are coded using MedDRA Version 19.0 or later and graded according to NCI-CTCAE v4.03.
Any patient with multiple occurrences of the same AE is counted only once in the AE category.

Pooled Analysis of Potential Immune-Related Adverse Events of Interest in Study BGB-A317_ Study_001:

All treatment-emergent adverse events (reported as of the 28 August 2017 data cutoff) considered to be potential immune-related AEs (irAEs) in Study BGB-A317_ Study_001 were analyzed.

For this analysis, phase 1a and 1b TEAEs from tislelizumab treatment were pooled. The pooled data were then combined with a pre-determined "hit-list" of Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms believed to represent immune-related events and symptoms.

Common potential irAEs ≥ 2% (all grade) included rash (11.9%), hypothyroidism (5.5%), rash maculo-papular (3.4%), and hyperthyroidism (3.4%).

1.3.2.1.2. Efficacy Results (13 January 2017 data cutoff date)

Duration of Treatment:

As of a 13 January 2017 data cutoff, a total of 111 patients had received BGB-A317 treatment in Parts 1-3 of the phase 1a component of Study BGB-A317_ Study_001.

Among the 22 patients treated in part 1 of phase 1a, the mean treatment duration was 109.2 days (range: 1 to 365). Treatment lasted longer for the 81 patients treated in part 2 of phase 1a, with mean durations of 142.4 days of treatment for patients receiving tislelizumab 2 mg/kg every 2 weeks and 191.9 days of treatment for patients receiving tislelizumab 5 mg/kg every 3 weeks (overall range: 1 to 471).

For the 8 patients treated in part 3 of phase 1a, the mean treatment duration was 54.1 days (range: 32 to 67).

Clinical Response**:**

Phase 1a

One of 22 (5%) patients in part 1 of phase 1a had a documented clinical response (a confirmed partial response [PR]); this patient was receiving tislelizumab 2 mg/kg. Meanwhile, 1/81 (1%) patients in part 2 of phase 1a had a documented complete response (CR) and 15/81 (19%) had a documented PR while receiving tislelizumab 2 mg/kg every 2 weeks.

The overall clinical response rates in the phase 1a component of Study BGB-A317_ Study_001 were 15% (95% CI: 5.71-29.84%) for the every 2 weeks regimen (combining 2 mg/kg and 5 mg/kg dosing) and 24% (95% CI: 12.36-40.30%) for the every 3 weeks regimen (combining 2 mg/kg and 5 mg/kg dosing).

Phase 1b

A total of 6/155 (4%) patients in the phase 1b component of the study had a confirmed clinical response; all were PRs (all dosed at 5mg/kg every 3 weeks). The overall clinical response rate in the phase 1b component was 4% (95% CI: 1.43- 8.23%).

1.3.2.2. Tislelizumab in the Treatment of Mature T- and NK-cell Neoplasms

High levels of FcγR-expressing myeloid derived suppressor cells (eg, M2 macrophage, MDSC) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated antibody-dependent cellular toxicity or antibody-dependent cellular phagocytosis depletion of effector T-cells (Gul and van Egmond 2015; Prieto et al 2015; Makarova-Rusher et al 2015; Beers et al 2016; Dahan et al 2015). Given absent FcγR binding and thereby minimal antibody-dependent cellular toxicity/antibody dependent cellular phagocytosis effect, tislelizumab may show better efficacy and lower toxicity in the treatment of mature T- and NK-cell neoplasms patients.

Finally, according to the latest data collected from the phase 1 Study BGB-A317_ Study_001, BGB-A317 monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies (Section 1.2.1.2).

1.3.2.3. Rationale for Selection of Tislelizumab Dose

The fixed dose of tislelizumab 200 mg every 3 weeks was selected on the basis of available PK, efficacy, and safety 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 every 2 weeks [n=62]; 2 mg/kg to 5 mg/kg every 3 weeks [n=41]) with no maximum tolerated dose defined at the highest dose examined. Efficacy has also been demonstrated in 23 of 266 (9%) evaluable patients to date, diagnosed with a variety of tumor types and treated according to a scheduled dose range. Specifically, rates of treatment-related AEs and serious AEs (SAEs) observed in patients taking 2 mg/kg and 5 mg/kg every 2 weeks and every 3 weeks were comparable suggesting no clear dose dependence across these regimens. Similarly, confirmed ORRs in patients treated with 2 mg/kg and 5 mg/kg every 2 weeks ranged between 5 and 14%, whereas they were between 17 to 37% for patents dosed 2 mg/kg and 5 mg/kg every 3 weeks.

According to phase 1a component PK data, serum concentrations of tislelizumab showed linear relationships with doses ranging from 0.5 mg/kg every 2 weeks to 10 mg/kg every 2 weeks. Because the clearance of tislelizumab was found to be independent of body weight, a 200 mg dose (body-weight adjusted dose between 3 and 4 mg/kg) administered every 3 weeks was expected to lead to serum exposures that fall between those observed after 2 mg/kg and 5 mg/kg doses. This prediction was corroborated with simulations conducted using the population PK analysis and further supported by preliminary PK data from 5 patients who were administered 200 mg every 3 weeks (Study BGB-A317_Study_001, phase 1a, part 3). Tislelizumab concentrations after the first 200 mg dose were in between the concentrations observed after 2 mg/kg and 5 mg/kg doses (in patients from Study BGB-A317_Study_001, phase 1a, parts 1, 2). Additionally, as shown by available data from Study BGB-A317_ Study_001 and BGB-A317-102, the PK profile of tislelizumab is consistent between Chinese patients and Caucasian patients.

Additionally, no unexpected treatment-related AEs occurred in the 200 mg fixed-dose cohort (Study BGB-A317_Study_001, phase 1a, part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n=4), 1 patient had a best overall response of stable disease (SD) and 3 patients had best overall responses of progressive disease. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg every 3 weeks.

In conclusion, tislelizumab 200 mg every 3 weeks is the recommended dose for pivotal studies, including BGB-A317-207.

1.4. Benefit-Risk Assessment

Patients with relapsed or refractory mature T- and NK-cell neoplasms represent a population with a great unmet medical need (Section 1.1). Median survival for relapsed or refractory NK/T-cell lymphoma is 5.5 months. There are no effective salvage regimens and the disease is invariably fatal.

An interim analysis of an ongoing clinical trial of PD-1 inhibition with pembrolizumab reported that seven patients with relapsed or refractory NK/T-cell lymphoma who had progressed following L-asparaginase therapy were treated with pembrolizumab and all responded, including five complete responses and two partial responses (Kwong et al 2017).

Tislelizumab is a second-generation PD-1 inhibitor designed to inhibit PD-1-mediated signaling with high specificity and affinity and either low or no antibody-dependent cellular toxicity or complement-dependent cytotoxicity effects in humans. More than 400 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination with tyrosine kinase inhibitors. The safety profile is consistent with known class effects of anti-PD-1 antibodies and includes mostly mild/moderate AEs. Very few severe (≥ Grade 3) irAEs have been observed; when they do occur, these events are generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion of the tislelizumab safety profile, please refer to the Investigator's Brochure. Given the unmet medical need and limited treatment options in this indication, the benefit-risk assessment based on available tislelizumab phase 1 data and published data in this patient population is considered favorable.

2. STUDY OBJECTIVES

2.1. Primary Objective

To evaluate efficacy, as measured by overall response rate and determined by investigator.

- For cohorts 1 and 2, overall response rate will be measured using the Lugano criteria (Cheson et al 2014) with Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) modification for immunomodulatory drugs (Cheson et al 2016).
- For cohort 3, overall response rate will be measured using the International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer (ISCL/EORTC) guidelines (Olsen et al 2011).

2.2. Secondary Objectives

For cohorts 1 and 2, efficacy measures will be determined using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016). For cohort 3, efficacy measures will be determined using the ISCL/EORTC guidelines (Olsen et al 2011).

- To evaluate efficacy, as determined by investigator and measured by the following:
  - Duration of response for all cohorts
  - Progression-free survival for all cohorts
  - Overall survival for cohorts 1 and 2
  - Rate of complete response or complete metabolic response for all cohorts
  - Time to response for all cohorts
  - Patient-reported outcomes (EQ-5D-5L and EORTC QLQ-C30) for all cohorts
- To evaluate safety and tolerability of tislelizumab for all cohorts

2.3. Exploratory Objectives

- [redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is a multicenter, prospective, non-randomized, open-label, phase 2 clinical study to evaluate the safety and efficacy of tislelizumab in patients with relapsed or refractory mature T-cell and NK-cell neoplasms. There will be three cohorts of patients: cohort 1 will include patients with relapsed or refractory extranodal NK/T-cell lymphoma (nasal or non-nasal type), with aggressive NK leukemia excluded; cohort 2 will include patients with relapsed or refractory mature T-cell neoplasms limited to peripheral T-cell lymphomas not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL); and cohort 3 will include relapsed or refractory patients with stage IB-IVB cutaneous T-cell lymphomas, limited to mycosis fungoides (MF) or Sèzary syndrome (SS).

Up to 70 patients will be enrolled into cohort 1, up to 50 patients into cohort 2 (up to 20 with PTCL-NOS, up to 20 with ALCL, and up to 10 with AITL), and up to 10 patients into cohort 3 for a total sample size of up to 130 patients. EBV status in cohorts 1 and 2 will be determined by EBV-encoded RNAs (EBER) in situ hybridization (ISH) from local pathology report or, if not previously performed, testing from archival or fresh tumor tissue. For cohort 3, EBV status is not mandatory. Patients' EBV status will be recorded if their local pathology report includes available EBV testing.

Due to the low prevalence of MF and SS in Asia-Pacific countries, cohort 3 will be available for accrual only in North America (US and Canada) and in the EU (Italy, France, and Germany). Further, recruitment of cohort 3 may be limited to sites and investigators that have the capability and expertise to diagnose, treat, and evaluate response in patients with MF and SS. This includes experience using the modified severity weight assessment tool (mSWAT) and local circulating Sèzary cell (CSC) testing by flow cytometry.

Enrollment will be held if no confirmed tumor responses are seen in the first 10 evaluable patients for cohort 1 and in the first 10 evaluable patients for cohort 2 subtypes of PTCL-NOS and ALCL, respectively, until the study Steering Committee can meet with the sponsor to discuss the risk/benefit ratio and make a joint decision to determine whether enrollment will be permanently discontinued in cohort 1 or subtype(s), based on the overall available data. If there is only one single confirmed tumor response among the first 10 evaluable patients for cohort 1 or cohort 2 subtypes of PTCL-NOS and ALCL, respectively, the Study Steering Committee and sponsor may also meet to discuss the risk-benefit ratio and determine whether it is appropriate to resume enrollment. If more than one confirmed tumor response is seen in the first 10 patients enrolled in cohort 1 or subtype(s), then enrollment of patients may resume.

Tislelizumab will be administered intravenously as a 200-mg infusion every three weeks. The primary efficacy endpoint is overall response rate (ORR) determined by investigator. Disease response for the primary endpoint for cohorts 1 and 2 will be assessed per the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory therapy (Cheson et al 2016). Disease response for cohort 3 for the primary endpoint will be assessed per ISCL/EORTC guidelines (Olsen et al 2011).

The study procedures will occur over a screening phase (up to 35 days); treatment phase (until disease progression, intolerable toxicity, or withdrawal of informed consent, whichever occurs first); safety follow-up phase (up to 90 days following last study treatment for all AEs and SAEs); and a survival follow-up phase (duration varying by patient).

Study treatment must commence within 5 days after screening assessments have been completed and study eligibility has been determined.

Each cycle consists of 21 days. A schedule of efficacy and safety assessments is presented in Appendix 11.

Study Assessments

Assessments of lymphoma status during the study include: disease-related constitutional symptoms; physical examination of lymph nodes, liver, spleen and skin; complete blood count (CBC); circulating EBV DNA (if EBV-positive by EBER ISH at screening); bone marrow examination (core biopsy); imaging studies including PET-CT and CT-based assessments; peripheral blood flow cytometry (cohort 3 only); and patient-reported outcomes (PROs).

For patients in cohorts 1 and 2, screening findings will determine whether patients are followed with PET-CT-based or CT-based assessments on study. That is, patients whose disease is not PET-avid will be followed by CT-based assessments alone while patients whose disease is PET-avid will be followed by an integration of PET-CT and CT-based assessments (as described in Section 5.4.1 and Appendix 11). Tumor assessments, including imaging studies, will be performed at screening, at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. Patients in cohort 2 whose disease is EBV-negative at screening are not required to undergo EBV DNA assessments during screening and study treatment periods.

For patients in cohort 3, since not all patients will have disease measurable by CT scan, patients will be assessed by ISCL/EORTC response criteria (Olsen et al 2011), which includes composite assessments of skin by mSWAT, as described in Appendix 14, lymph nodes and visceral disease assessed by PET and/or CT, and blood tumor burden of CSC by flow cytometry. Assessments will be performed starting at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. Patients who are suspected to have progression at Week 12 will have a confirmatory response assessment at Week 16 using the same assessment(s) that indicated progression (eg, if mSWAT but not CT scan indicates progression at Week 12, then only mSWAT is required at Week 16).

CT-based assessments should be of diagnostic quality with contrast administered. Patients with PET-avid disease in cohorts 1 and 2 and patients with nodal disease in cohort 3 undergoing a tumor assessment at a timepoint when PET-CT is required should ideally undergo a diagnostic quality, contrast-enhanced CT during a single visit combined with PET. If that is not possible, then a diagnostic quality, contrast-enhanced CT can be done as a separate study from PET-CT. MRI may be substituted for diagnostic quality, contrast-enhanced CT for patients with serious contrast allergy. Assessment of tumor response will be made by the investigator.

All patients should remain on study treatment until disease progression is confirmed by the investigator.

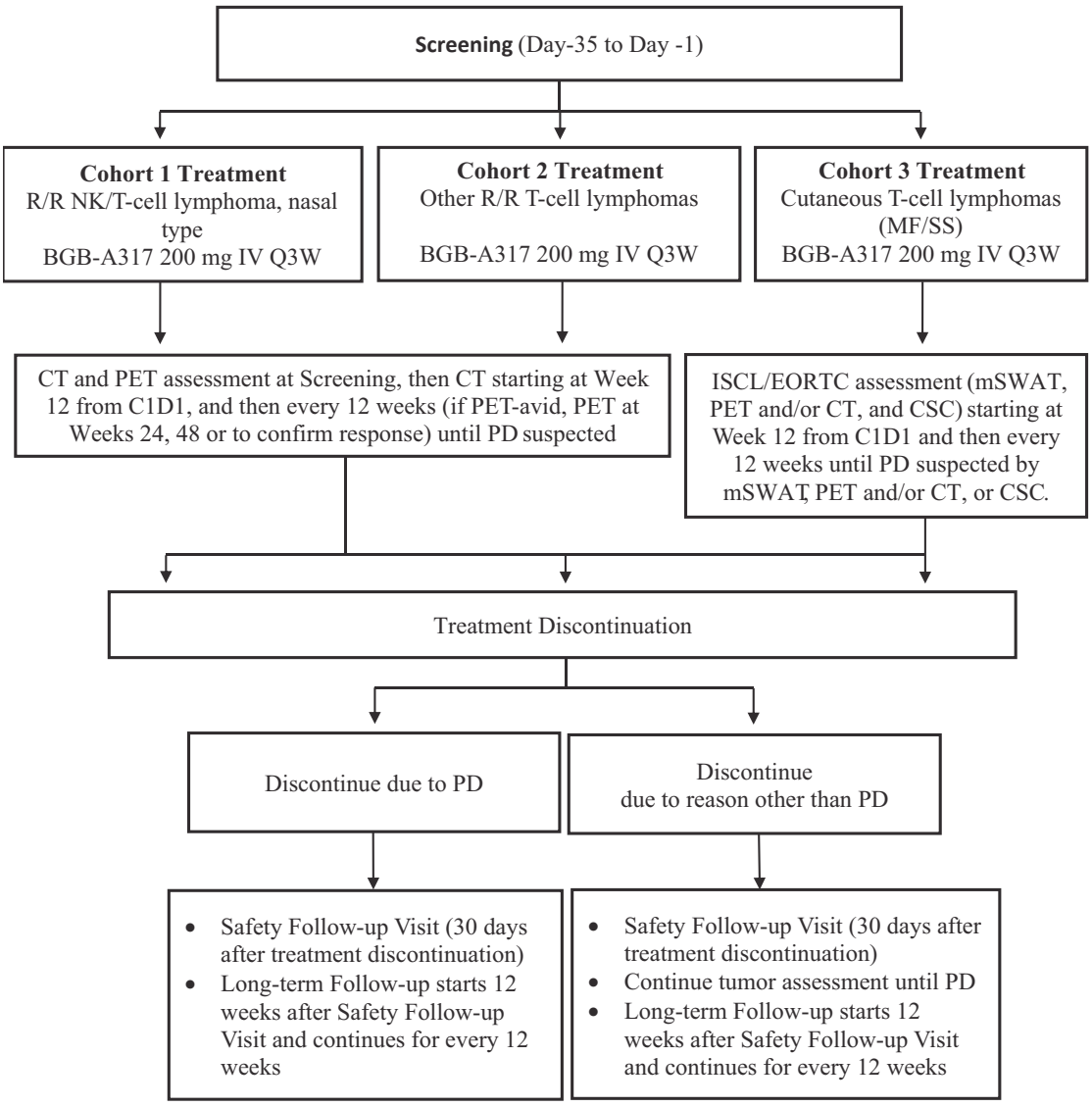
Patients assessed as having a CR by imaging who also had bone marrow involvement at screening will have a bone marrow examination to confirm a CR.

Assessments of safety will include AEs, SAEs, clinical laboratory tests, physical examinations, pulmonary and cardiac function tests, ECGs, ECOG performance status, vital signs, and ophthalmologic examinations. AEs will be graded for severity per the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4.03. An independent data monitoring committee (IDMC) will periodically monitor safety data.

3.2. Study Schematic

The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



Abbreviations: C1D1 = Cycle 1 Day 1; CSC = circulating Sezary cell; CT = computed tomography; ISCL/EORTC = International Society for Cutaneous Lymphomas/European Organization of Research and Treatment of Cancer; IV = intravenous; MF = mycosis fungoides; mSWAT = modified severity weight assessment tool; NK = natural killer; PD = progressive disease; PET = positron emission tomography; Q3W = every 3 weeks; R/R = relapsed/refractory; SS = Sezary syndrome.

The initial infusion (C1D1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for at least 1 hour afterwards during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of > 30 minutes will be required.
For cohorts 1 and 2, patients will undergo PET-CT assessment at screening. Patients whose disease is not PET-avid at screening will be followed by CT-based assessments alone while patients whose disease is PET-avid at screening will be

followed by an integration of PET-CT and CT-based assessments (ie, PET-CT assessments will be performed at week 24 and week 48, and at the time of suspected response, disease progression, or indeterminate response [IR] as follow-up evaluation within 12 weeks to confirm or refute true disease progression.)
For cohort 3, not all patients will have disease that is measurable by CT scan, so patients will be followed by ISCL/EORTC response criteria (Olsen et al 2011), which includes composite assessments of skin by mSWAT, lymph nodes and visceral disease assessed by CT, and blood tumor burden of CSC by flow cytometry. At the discretion of the investigator and with patient consent, patients may be treated beyond disease progression under protocol-defined conditions (Section 5.4.4).

3.3. Blinding

Treatment with tislelizumab will be open-label.

3.4. Duration of Study

Total duration of study participation will vary by patient.

The total duration of this study is expected to be approximately 3 years, assuming an expected enrollment duration of 24 months and maximum duration of tislelizumab of 12 months after the last enrolled patient.

Each study phase is further discussed in Section 5.

4. SELECTION OF STUDY POPULATION

The specific eligibility criteria for the selection of up to 70 patients enrolled into cohort 1, up to 50 patients enrolled into cohort 2, and up to 10 patients enrolled into cohort 3 are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

To be eligible to participate in this study, a patient must meet all of the following criteria:

1. Histologically confirmed diagnosis of relapsed or refractory, mature T-cell and NK-cell neoplasms based on the WHO 2016 classification of tumors of hematopoietic and lymphoid tissue. Patients will be allocated to one of three cohorts based on their histologic diagnosis:
    - Cohort 1: Extranodal NK/T-cell lymphoma (nasal or non-nasal type)
        - Patients with aggressive NK leukemia are excluded
    - Cohort 2: Other mature T-cell neoplasms, limited to the following histologies:
        - Peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS)
        - Angioimmunoblastic T-cell lymphoma (AITL)
        - Anaplastic large cell lymphoma (ALCL)
    - Cohort 3: Stage IB-IVB cutaneous T-cell lymphomas, limited to the following histologies (Appendix 15):
        - Mycosis fungoides (MF)
        - Sèzary syndrome (SS)
2. Male or female ≥ 18 years of age at the time of informed consent (or acceptable age according to local regulations, whichever is older)
3. Previously received 1 or more appropriate systemic therapies (eg, non-anthracycline-based regimens such as L-asparaginase-based therapy) for cohort 1 or combination chemotherapy (eg,

CHOP, EPOCH, or similar therapy) for cohort 2. Radiation therapy alone would not be acceptable as previous therapy.

- For patients with relapsed or refractory anaplastic large cell lymphoma, regardless of anaplastic lymphoma kinase (ALK) status, must have received prior therapy with brentuximab vedotin (applicable only to countries where brentuximab vedotin received marketing approval)

4. Disease progression during or after completion of most recent therapy or refractory disease. Refractory disease is defined as failure to achieve CR or PR to most recent therapy, and most recent therapy was an appropriate systemic therapy for mature T-cell or NK-cell lymphoma
5. For cohorts 1 and 2, patients must have lesions that are measurable by imaging, where measurable is defined as ≥ 1 lesion that is > 1.5 cm for nodal lesions and > 1 cm for extranodal lesions.
   For cohort 3, patients are not required to have measurable disease by imaging.
6. Availability of either unstained tissue (block or unstained slides) or stained slides, and pathology report for central confirmation of mature T-cell or NK-cell lymphoma. If stained slides or unstained tissue (block or unstained slides) are not available or are insufficient, a fresh tumor tissue sample is mandatory for central pathology. Central pathology confirmation is not required prior to enrollment.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Table 3)
8. Life expectancy ≥ 6 months
9. Patients must have forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) > 60% by pulmonary function test (PFT), carbon monoxide diffusion capacity (DLCO) > 60% predicted value, and FEV_1 and FVC > 50% predicted value; all PFTs must be obtained within 4 weeks prior to the first dose of tislelizumab
10. Adequate organ function defined as:
    - Absolute neutrophil count (ANC) > 1000/mm^3 (without growth factor support within 7 days of ANC measurement)
    - Platelet > 50,000/mm^3 (without growth factor support or transfusion within 7 days of platelets measurement)
    - Hemoglobin > 80 g/L (prior transfusion is acceptable)
    - Creatinine clearance ≥ 30 ml/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection) (Appendix 9)
    - Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase, and alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≤ 3.0 × upper limit of normal (ULN)
    - Serum total bilirubin < 2.0 × ULN (unless documented Gilbert's syndrome)
11. Female patients of childbearing potential must be willing to use a highly effective method of birth control/contraception for the duration of the study, and for at least 120 days after the last dose of tislelizumab and have a negative serum pregnancy test within 7 days of the first dose of study drug. Please refer to Appendix 4 for a list of acceptable birth control/contraception methods and contraceptive guidelines.

12. Non-sterile males must be willing to use a highly effective method of birth control/contraception for the duration of the study and for at least 120 days after the last dose of tislelizumab:
    - Sterile males are those for whom azoospermia, in a semen sample examination, has been demonstrated as definitive evidence of infertility
    - Males with "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study
13. Ability to provide written informed consent and can understand and comply with the requirements of the study

4.2. Exclusion Criteria

To be eligible to participate in this study, a patient cannot meet any of the following exclusion criteria:

1. Known central nervous system involvement by leukemia or lymphoma
2. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 agent
3. Meets one of the following scenarios for hematopoietic stem cell transplantation and/or chimeric antigen receptor T-cell (CAR-T) therapy:
    - Is eligible for autologous or allogeneic stem cell transplantation, unless patient has refused transplantation
    - Has undergone prior allogeneic hematopoietic stem cell transplantation or organ transplantation
    - Has received autologous stem cell transplantation within 6 months prior to first dose of study drug
    - Has received CAR-T therapy within 12 months prior to the first dose of study drug
4. Has received:
    - Systemic chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks (or 5 half-lives, whichever is shorter) prior to study Day 1
    - Recent treatment with another monoclonal antibody within 4 weeks prior to study Day 1
    - Investigational treatment or device within 4 weeks (or 5 half-lives, whichever is shorter) prior to study Day 1
    - For cohort 3 patients, phototherapy within 2 weeks or any topical therapy within 1 week prior to study Day 1
    - Or has not recovered from AEs (ie, ≤ Grade 1 or baseline level) due to prior therapy. (Note: Patients with alopecia or ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study if all other criteria are met).
5. Concurrent or prior malignancy within the past 3 years, except for curatively treated basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast, or localized Gleason score 6 or lower prostate cancer
6. Active autoimmune diseases or history of autoimmune diseases that may relapse (see Appendix 3)
   Note: Patients with the following diseases are not excluded and may proceed to further screening:

- Type I diabetes under control
- Hypothyroidism (provided it is managed with hormone replacement therapy only)
- Controlled celiac disease
- Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia), except when such diseases significantly interfere with response assessment of patients in cohort 3
- Any other disease that is not expected to recur in the absence of external triggering factors

7. Has known history of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis, acute lung diseases or evidence of dyspnea at rest or pulse oximetry of < 92% while breathing room air
8. Has any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 14 days before study drug administration. Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:
    - Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    - Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption, except when given for treatment of MF or SS
    - Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen
9. Has a known active TB (Bacillus Tuberculosis) infection
10. Known infection with HIV, human T-cell lymphotropic virus-1, -2, or serologic status reflecting active hepatitis B or C infection as follows:
    - Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb). Patients with presence of HBcAb, but absence of HBsAg, are eligible only if hepatitis B virus (HBV) DNA is undetectable by an assay with sensitivity ≤ 20 IU/mL. If so, patients may either undergo regularly scheduled monitoring of HBV DNA or less frequent monitoring of HBV DNA while on prophylactic antiviral medication as defined by regional standard of care.
    - Presence of hepatitis C virus (HCV) antibody. Patients with presence of HCV antibody are eligible only if HCV RNA is undetectable.
11. Active fungal, bacterial, and/or viral infection requiring systemic therapy
12. Vaccination with a live vaccine within 35 days prior to the first dose of study drug
13. Clinically significant cardiovascular disease including the following:
    - Myocardial infarction within 6 months before screening
    - Unstable angina within 3 months before screening
    - New York Heart Association Classification III or IV congestive heart failure (Appendix 5)

- History of clinically significant arrhythmias (eg, sustained ventricular tachycardia, ventricular fibrillation, torsades de pointes)
- QTcF > 480 msecs based on Fridericia's formula
- History of Mobitz II second-degree or third-degree heart block without a permanent pacemaker in place
- Uncontrolled hypertension as indicated by a minimum of 2 consecutive blood pressure measurements showing systolic blood pressure > 170 mm Hg and diastolic blood pressure > 105 mm Hg at screening

14. Major surgery within 4 weeks of the first dose of study drug
15. Ongoing alcohol or drug addiction
16. Underlying medical or social conditions that, in the opinion of the investigator and/or medical monitor, will render the administration of study drug hazardous or obscure the interpretation of safety or efficacy results
17. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment
18. Has hypersensitivity to tislelizumab or any of its excipients
19. History of severe hypersensitivity reactions to other monoclonal antibodies
20. Concurrent participation in another therapeutic clinical trial

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments in Appendix 11.

All assessments must be performed and documented in the medical record and electronic case report form (eCRF) for each patient.

5.1. Informed Consent Form and Screening

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures (refer to Appendix 11 for details).

At the first screening visit, study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. Study site personnel must obtain signed informed consent before any study-specific procedures are conducted unless the procedures are part of routine standard of care, and must document the informed consent process in the patient's clinical record. Informed consent may be obtained before the 35-day screening period. Consent must be obtained using the most current version of the form approved by the ethics committee.

Screening evaluations will be performed within the screening period, which is defined as 35 days prior to enrollment. For bone marrow core biopsy, echocardiogram/multigated acquisition scan, and comprehensive eye examination (including optical coherence tomography or equivalent), screening evaluations may be performed within 90 days prior to enrollment, subject to review and agreement by the medical monitor or designee. Repeating the screening procedures or tests is allowed if the patient did not previously meet the inclusion and exclusion criteria or if needed in order to have a documented result

within the protocol-specified screening window. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 35 days prior to enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests.

Results of standard-of-care tests or examinations for bone marrow core biopsy, echocardiogram/multigated acquisition scan, and comprehensive eye examination (including optical coherence tomography or equivalent) performed prior to obtaining informed consent and ≤ 90 days prior to enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests, subject to review and agreement by the medical monitor or designee.

The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

5.1.1. Subject Numbering

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

5.1.2. Medical History and Demographic Data Collection

Medical history should include any history of clinically significant disease, surgery, or cancer history (including prior anticancer therapies and procedures); reproductive status (ie, of childbearing potential or no childbearing potential [Appendix 4]); history of alcohol and tobacco consumption (ie, presence or absence); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 35 days before the first dose. These data will be collected and captured in the eCRF for enrolled patients.

Demographic data will include age, gender, and self-reported race/ethnicity.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response, and reason for discontinuation.

New or worsened clinically significant abnormalities are to be recorded as AEs on the Adverse Event eCRF. Refer to Section 8.4.1 regarding AE definitions and reporting and follow-up requirements.

5.1.3. Confirmation of Eligibility

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

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and email it to the medical monitor or designee to agree with the enrollment in writing. Study site personnel should ensure that the final Eligibility Packet is in the patient's file before proceeding with study procedures.

Either unstained tissue (block or unstained slides) or stained slides, together with pathology report, should be sent to central pathology laboratory for confirmation of tissue diagnosis. If unstained tissue (block or unstained slides) or stained slides are not available, collection of a fresh tumor biopsy at screening is

mandatory. Central pathology confirmation is not required prior to enrollment. If an archival tissue sample is available, it should be collected for central pathology and other biomarker analysis. Refer to Section 5.4.7 for details.

5.2. Study Treatment

Unless otherwise described, baseline refers to Cycle 1 Day 1 measure before the first study drug administration.

After completing all screening activities, patients confirmed eligible will be enrolled to receive open-label tislelizumab treatment as follows:

- Tislelizumab 200 mg intravenously every 3 weeks until disease progression according to the Lugano criteria (Cheson et al 2014) with the LYRIC modification for immunomodulatory therapy (Cheson et al 2016) for cohorts 1 and 2 patients or according to ISCL/EORTC guidelines (Olsen et al 2011) for cohort 3 patients, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

In all cohorts, treatment beyond investigator-assessed Lugano-defined disease progression with the LYRIC modification or ISCL/EORTC-defined disease progression is permitted provided that the patient a) has investigator-assessed clinical benefit and b) is tolerating study drug. Specific requirements for post-progression continuation of patients treated with tislelizumab, including the need to sign an additional informed consent, are described in Section 5.4.4.

5.2.1. Timing of Assessments During Study Treatment

A study visit may be scheduled on any day within a specified study week. For any given day within the study week, the visit window is ± 7 days (ie, 7 days before or after the given day) unless otherwise stated (see Appendix 11). The minimum amount of time between doses is 10 days. Study drug supplies must be considered when scheduling visits during windows. Procedures for a given visit may be split across the window to allow for drug resupply and completion of study procedures.

All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date, with subsequent dosing rescheduled on a 21-day interval from Cycle 1 Day 1, accordingly.

5.3. Safety Assessments

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per NCI-CTCAE v4.03), and laboratory abnormalities. Physical examinations, vital signs, ECOG performance status change, pulmonary and cardiac function tests, electrocardiogram (ECG), and ophthalmologic examination results will also be used for safety assessment.

5.3.1. Physical Examinations

A complete physical examination, including an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems is required to be performed at screening. Any abnormality identified at baseline will be recorded on the Medical History eCRF with appropriate disease/condition terms. Height (baseline only) and weight will be measured and recorded in the eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed. Changes from baseline will be recorded in patient notes.

5.3.2. Vital Signs Assessment

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

For the first infusion of tislelizumab, the patient's vital signs will be assessed within 60 minutes before the infusion, every 15 minutes or per site standard of care during the infusion, and 30 minutes after the infusion of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during the infusion and 30 minutes after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. Refer to Section 8.9.1 regarding management of infusion-related reactions.

Investigator may perform additional or more frequent blood pressure assessments if clinically indicated.

5.3.3. Eastern Cooperative Oncology Group Performance Status Grading

ECOG performance status (Table 3) will be assessed at the Screening visit; pre-treatment on Cycle 1 Days 1, 8, and15; pretreatment on Day 1 of each subsequent treatment cycle; and Safety Follow-up visit.

Table 3: Eastern Cooperative Oncology Group Performance Status – Grading System

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

5.3.4. Pulmonary Function Tests

Pulmonary function tests include spirometry and lung diffusion capacity. Screening evaluations must be performed within 4 weeks prior to first dose of tislelizumab.

5.3.5. Electrocardiograms and Cardiac Function Tests

12-lead ECG recordings are required at screening, safety follow-up, and as clinically indicated. The screening ECG must be a triplicate ECG recording (3 readings in rapid succession and not more than 2 minutes apart). All ECG recordings should be performed after the patient has been resting for at least 10 minutes, and a repeat ECG should be performed to confirm findings, if any.

Cardiac function is assessed by either echocardiography or multigated acquisition scan. Screening evaluations may be performed within 90 days prior to enrollment, subject to review and agreement by the medical monitor or designee.

5.3.6. Ophthalmologic Examination

Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test, including a dilated fundoscopic examination) will be assessed during the screening period. Screening evaluations may be performed within 90 days prior to enrollment, subject to review and agreement by the medical monitor or designee. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 90 days prior to enrollment may be used for the screening evaluation, subject to review and agreement by the medical monitor or designee. Patients will undergo repeat assessments approximately every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until the patient discontinues from study treatment.

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

5.3.7. Concomitant Medications Review

Record any new medications, changes in ongoing medications or procedures, and medications discontinued within 35 days before the first visit in Cycle 1 and since the prior study visit, thereafter.

5.3.8. Adverse Event Collection

All SAEs will be collected after informed consent has been signed but prior to administration of the study drug. All AEs and SAEs, regardless of relationship to study drug, will be recorded until up to 90 days after the last dose of study treatment. Beyond 90 days after treatment discontinuation, all drug-related SAEs will be recorded by investigator until patient death, or lost to follow-up, whichever occurs first. 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. The AE reporting period is defined in Section 8.7.1.

At the end of treatment, ongoing AEs will be followed until the event has resolved to baseline level or Grade 0-1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AEs.

The accepted regulatory definition for an AE is provided in Section 8.4.1. Important additional requirements for reporting SAEs are explained in Section 8.7.3 and Section 8.8.

5.4. Efficacy Assessments

5.4.1. Antitumor Activity and Clinical Response Assessment

For patients in cohorts 1 and 2, response will be assessed by investigator and categorized per the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016). The primary endpoint will be ORR based on investigator assessment. Response parameters will include: disease-related constitutional symptoms; physical examination of lymph nodes, liver, and spleen; CBC; circulating EBV DNA (if EBV-positive by EBER ISH at screening); bone marrow examination; imaging studies including PET-CT- and CT-based assessments; and PROs. Tumor assessments, including imaging studies, will be performed at screening, at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. In the

event of a treatment delay, disease assessments are to continue per the Schedule of Assessments (Appendix 11).

For patients in cohort 3, response will be assessed by investigator and categorized per ISCL/EORTC guidelines for response assessment of patients with mycosis fungoides or Sèzary syndrome (Olsen et al 2011). The primary endpoint will be ORR based on investigator assessment. Response parameters will include skin assessment by mSWAT, lymph node or viscera involvement by PET and/or CT, and peripheral blood by flow cytometry. Not all response assessments will be utilized depending on the presence or absence of measurable disease on CT or circulating Sèzary cells. Overall response will be determined by Global Response Score (Table 5, Appendix 13).

Tumor assessments, including imaging studies as required for those patients with measurable disease by CT, will be performed starting at Week 12 from Cycle 1 Day 1, then every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, then yearly thereafter. If progression is suspected at Week 12, an additional response assessment will be performed at Week 16 to rule in or out a tumor flare. Patients with suspected progression after Week 12 should have all response assessments performed even if not at a scheduled response assessment timepoint to confirm progression.

5.4.2. Exam of Liver, Spleen, Lymph Nodes, and Skin

For patients in cohorts 1 and 2, assessments for the enlargement of liver, spleen, and lymph nodes are included in the physical examination and will be evaluated at screening, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and thereafter yearly until disease progression, and during safety follow-up and long-term follow-up.

For patients in cohort 3, examination of the skin is included in the physical examination reported at each study visit. Formal assessment for response by mSWAT score (Appendix 14) will be performed starting on Cycle 1 Day 1, at Week 12 from Cycle 1 Day 1, then every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, then yearly thereafter. If progression is suspected at Week 12, an additional response assessment will be performed at Week 16 to rule in or out a tumor skin flare. Patients with suspected progression after Week 12 should have all response assessments performed even if not at a scheduled response assessment timepoint to confirm progression.

5.4.3. Positron Emission Tomography (PET)-Computed Tomography (CT) and CT with Contrast

Cohorts 1 and 2

Patients in cohorts 1 and 2 must have a screening (within 35 days prior to enrollment) PET-CT scan with contrast of neck, chest, abdomen, and pelvis and any other disease sites. For patients in cohort 1, the screening PET-CT should evaluate the nasal cavity, hard palate, anterior cranial fossa, nasopharynx and any other site of known or suspected disease. Screening findings will determine whether patients are followed with PET-CT-based or CT-based assessments on study. That is, patients whose disease is not PET-avid will be followed by CT-based assessments alone while patients whose disease is PET-avid will be followed by an integration of PET-CT and CT-based assessments.

Ideally, contrast-enhanced CT should occur during a single visit combined with PET-CT. Combined PET-CT may be used in lieu of a CT with contrast only if the CT of the combined PET-CT has been performed with diagnostic quality and contrast is administered. An MRI may be used in place of CT only for patients who cannot undergo CT due to contrast allergy. All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's course on study.

A central imaging vendor will be utilized for PET-CT, CT, and MRI scans and reports obtained during the study. De-identified copies of all scans and radiology reports (including those from screening) must be provided to the sponsor or designee (eg, central imaging vendor).

Tumor assessments, including imaging studies, will be performed at screening, at Week 12 from Cycle 1 Day 1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. Patients in cohorts 1 and 2 must undergo PET-CT scan during screening. Patients whose disease is not PET-avid at screening will be followed by CT-based assessments alone. Patients whose disease is PET-avid at screening will be followed by an integration of PET-CT and CT-based assessments as follows:

- PET-CT scans are required at screening, Week 24, Week 48, and for any of the following reasons: to confirm a result on CT scan (CR/PR or disease progression) or for patients who are classified as having an indeterminate response (IR) as a follow-up evaluation within 12 weeks in order to confirm or refute true disease progression. For example, if a Week 12 CT scan result is consistent with a new finding of CR, PR or IR, then a PET is required. However, if a Week 24 PET result is consistent with polymyalgia rheumatica (PMR), no additional PET is required at Week 36 unless a CR is suspected.
- CT scans with contrast are required at all other tumor response assessments

Cohort 3

Patients with mycosis fungoides or Sezary syndrome might not have measurable disease on imaging studies; given this, response assessments will be performed per ISCL/EORTC consensus recommendations to allow assessment without imaging in select patients (Olsen et al 2011).

All patients will undergo diagnostic-quality PET and/or CT imaging of the chest, abdomen, pelvis, and any other known extracutaneous disease site at screening. If patients do not have measurable disease at screening (including those with non-measurable disease), imaging will only be obtained while on study for response assessments if progression is suspected by the investigator. Imaging is not required to confirm CR, PR, or SD for patients with absent or nonmeasurable disease by imaging. Patients with disease that involves the lymph nodes will continue to undergo PET imaging in addition to CT imaging while on study.

Patients with measurable disease at screening will undergo CT imaging of the chest, abdomen, pelvis, and any other known extracutaneous disease site starting at Week 12 from Cycle 1 Day 1, every 12 weeks until week 96, every 24 weeks for an additional 96 weeks, then yearly until disease progression. If progression is seen at Week 12 imaging, imaging will be repeated at Week 16 to rule in or out a tumor flare. Imaging should be performed at any time point where disease progression is suspected after Week 12.

General Considerations

If there is a concern about early progression, imaging at the end of Cycle 1 to document progression is recommended.

If for some unexpected reason, the protocol-specified imaging study is not able to be done within the specified time window, but there is another method available of assessing target and nontarget lesions in alignment with the Lugano or ISCL/EORTC criteria, this must be discussed and approved by the medical monitor prior to the tumor assessment.

In rare instances, the timing of a patient's scans may fall outside of the imaging procedure window specified in the Schedule of Assessments (Appendix 11) – for example, due to out-of-town travel or other

unforeseen circumstances. Rare occurrences of missing scans or scans completed outside the procedure window will not necessarily be considered as a protocol deviation; the sponsor will make the final determination.

5.4.4. Disease Progression with Immune Checkpoint Inhibitors

The information in this section should be referenced for patients in cohorts 1 and 2 only.

During treatment with immune checkpoint inhibitors such as with tislelizumab, pseudo-progression (aka delayed-response or tumor flare) may occur due to immune cell infiltration and other mechanisms as manifested by an apparent increase of existing tumor masses or appearance of new tumor lesions. A modification of the Lugano tumor response criteria, named LYRIC, was created to address this phenomenon and prevent patients being prematurely removed from a treatment from which they may benefit (Cheson et al 2016). The term, "indeterminate response" was created to identify lesions until confirmed as either true disease progression or pseudo-progression by either biopsy and/or subsequent imaging. Per LYRIC, if a patient is assessed as having IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. If a patient is assessed as having any response other than PD (ie, SD, PR, or CR) at a subsequent time point after the IR assessment, the prior designation of IR will remain an IR.

Patients with suspected pseudo-progression can continue study treatment provided they meet the following criteria:

a) Absence of clinical symptoms and signs of disease progression (including worsening laboratory values)

b) Stable ECOG performance status

c) Absence of rapid progression at critical anatomical sites (eg, cord compression) that necessitates urgent medical intervention

Follow-up imaging and/or biopsy for patients who have a diagnosis of radiographic disease progression must be performed no later than 12 weeks (or earlier if clinically indicated, eg, 4 to 8 weeks) beyond the initial determination of IR.

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

Tumor assessments are to be performed on schedule regardless of whether study treatment has been administered or held.

5.4.5. Bone Marrow Examination

Bone marrow core biopsy is required under the following conditions during the treatment period: during screening (unless completed within 90 days prior to enrollment, subject to review and agreement by the medical monitor or designee) to assess bone marrow involvement of lymphoma and to confirm a CR in patients with bone marrow involvement at screening. All pathology samples will be analyzed locally, with results reported to the sponsor.

5.4.6. Circulating EBV DNA

For patients in cohorts 1 and 2, peripheral blood samples will be collected at specified times as described in the Schedule of Assessments (Appendix 11) to be used for the evaluation of surrogate efficacy

measures, such as, but not limited to, circulating levels of EBV DNA.

Circulating EBV DNA will be quantified with quantitative polymerase chain reaction. Patients in cohort 2 whose disease is determined to be EBV-negative by EBER ISH at screening are not required to undergo subsequent circulating EBV DNA assessments during screening and study treatment periods.

5.4.7. Biomarker Assessment Procedures

Shipping, storage, and handling of tumor tissue and blood samples for central pathology confirmation and assessment of other biomarkers will be managed through a central laboratory. Refer to the Laboratory Manual for details of sample handling.

Either approximately 20 stained slides or unstained tissue (formalin-fixed paraffin-embedded [FFPE] block with tumor tissue or unstained slides), together with a pathology report, are required to be sent to the central laboratory for central confirmation of diagnosis. In the absence of available unstained tissue (FFPE block or unstained slides) or stained slides, collection of a fresh tumor biopsy at screening is mandatory for central pathology. For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

After central pathology review is completed, the remaining tumor tissues (FFPE block with tumor tissue or unstained FFPE slides) will be collected, if available, to assess potential predictive biomarkers, such as but not limited to PD-L1 expression, gene expression profiling, and tumor-infiltrating lymphocyte status. Furthermore, samples collected from cohort 3 patients without a reported EBER status on their local pathology report will be assessed for EBV status.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable.

5.4.8. Patient-Reported Outcomes

Patient-reported outcomes (PROs) will continue to be assessed until disease progression, death, or withdrawal of consent, regardless of study treatment discontinuation. Patients in all cohorts will be asked to complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires per the Schedule of Assessments (Appendix 11) before study drug is administered.

EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome (The Euro Qol Group 1990; Herdman et al 2011). Patients will self-rate their current state of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression by choosing 1 of 5 possible responses that record the level of severity (no problems, slight problems, moderate problems, severe problems, or extreme problems) within each dimension. The questionnaire also includes a visual analog scale to self-rate general health state on a scale from "the worst health you can imagine" to "the best health you can imagine." A sample questionnaire is provided in Appendix 6 as an example only.

EORTC QLQ-C30

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients (Fayers et al 2001). It is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. The EORTC QLQ-C30 includes 30 separate questions (items). The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general, and specifically in non-Hodgkin lymphoma patients. It is a reliable and valid measure of PRO in cancer patients and takes about 11 minutes to administer. A sample questionnaire is provided in Appendix 7 as an example only.

5.5. Clinical Laboratory Tests

Samples for protocol-specified hematology, chemistry, thyroid function test, pancreatic enzymes, and coagulation profiles will be evaluated by a local laboratory (see list in Appendix 12). A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels are provided in the laboratory manual.

Laboratory results required for treatment decisions or for patient monitoring may be performed locally and entered into the eCRF. Samples for pregnancy testing and hepatitis B and C testing will be performed locally where available or in specialized laboratories, if needed. Submission of samples to specialized laboratories for HBV DNA testing will be required if the local laboratory is unable to achieve sensitivity for HBV DNA ≤ 20 IU/mL.

Clinical laboratory tests will be performed at the timepoints specified in the Schedule of Assessments (Appendix 11) and may also be performed as medically necessary. At screening, if hematology, serum chemistry (excluding CK and CK-MB), and liver function tests are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug administration. If these tests are conducted within 72 hours of the first study drug administration, they do not need to be repeated on Cycle 1 Day 1. On Cycle 1 Day 1, laboratory assessments should be done before study drug administration. 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 (eg, cause study discontinuation or constitutes in and of itself a SAE) should be recorded on the AEs eCRF.

Hematology

CBC with differential is required to be performed locally at every scheduled visit during the treatment phase and during Safety Follow-up (see Appendix 11). CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential including neutrophils (including bands, if available), lymphocytes, monocytes, eosinophils, and basophils. In the event of ≥ Grade 3 neutropenia or thrombocytopenia that developed on study treatment, the frequency of CBC monitoring will be conducted as often as clinically indicated, according to the investigator's medical judgement, to ensure patient safety, and close monitoring should occur until toxicity resolves to ≤ Grade 2. Those patients who discontinue study drug for reasons other than radiographically confirmed disease progression will continue to undergo efficacy assessments until radiographically confirmed disease progression.

Chemistry

Serum chemistry includes sodium, potassium, chloride, bicarbonate or CO_2 (or if neither are available, CO_2 combining power) glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total bilirubin, total protein, albumin, ALT, AST, lactate dehydrogenase, and alkaline phosphatase. Assessment should be as indicated in Appendix 11 and performed locally. In the event of ≥ Grade 3 clinical chemistry toxicity that developed on study treatment, the frequency of clinical chemistry monitoring will be conducted as often as clinically indicated, according to the investigator's medical judgement, to ensure patient safety, and close monitoring should occur until toxicity resolves to ≤ Grade 2. All patients will have creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB) testing at screening and before Cycles 1 to 3 dosing, all predose clinic visits from Cycle 4 onwards, and at the end of treatment and Safety Follow-up visits. In the event that CK-MB fractionation is not able to be evaluated using the local laboratory, troponin I and/or troponin T should be assessed instead.

Thyroid Function Tests

Free T3, free T4, and thyroid-stimulating hormone (TSH) will be performed locally. Assessment should be as indicated in Appendix 11.

Liver Function Tests

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and total bilirubin will be performed locally. Assessment should be as indicated in Appendix 11.

Pancreatic Enzymes

Pancreatic enzymes (amylase and lipase) will be tested locally if clinically indicated while on treatment. Assessment should be as indicated in Appendix 11.

Coagulation

The coagulation profile includes prothrombin time, which will also be reported as international normalized ratio and activated partial thromboplastin time. The coagulation profile will be performed locally at screening and if clinically indicated while on treatment.

Hepatitis B and C Testing

Hepatitis B/C serologic markers and/or viral load will be tested at screening.

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

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

The hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive; patients with detectable level of HCV RNA (≥15 IU/mL) are not eligible. Patients with positive HBsAg and/or detectable HBV DNA are not eligible.

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

- Undergo HBV DNA testing by PCR every other cycle beginning in Cycle 2 (ie, Cycles 2, 4, 6, 8 etc.) without beginning prophylactic antiviral medication OR
- Begin prophylactic dosing of antiviral therapy according to the regional standard of care. Patients will undergo HBV DNA testing by PCR every 4 cycles beginning in Cycle 4 (ie, Cycles 4, 8, 12 etc.). Medications recommended and excluded are described in Section 7.2.1. It is recommended that antiviral therapy be initiated at least 2 weeks before the first dose of study treatment and continue until 6 months after discontinuation of study treatment. Patients may enter the study on HBV antiviral medication according to the regional standard of care.

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

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

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

The medical monitor should be informed of any suspected hepatitis B or hepatitis C re-activation.

Table 4 below, shows how the results for, HBV/HCV, and HBV/HCV testing at screening relate to inclusion and exclusion criteria.

Table 4: Active Hepatitis B (HBV) or Hepatitis C (HCV) Infection (Detected Positive by PCR)

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

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

HIV/HTLV-1,-2 Testing (For Germany Only)

All patients across all regions with known HIV/HTLV-1,-2 infection are excluded from participating in the study. In Germany, for patients who do not have known HIV/HTLV-1,-2 infection, HIV/HTLV-1,-2 testing will be performed at screening as indicated in Appendix 11. All patients who test positive will not be eligible for the study.

Pregnancy Test

A serum pregnancy test will be performed at Screening within 7 days of the first study drug administration in women of childbearing potential. Any female patient who is pregnant will not be eligible for the study. Urine pregnancy tests will be performed locally on Day 1 of every cycle starting with Cycle 2. Pregnancy tests must be continued every cycle for at least 120 days after the last dose of study drug. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Serum pregnancy tests may be substituted for urine pregnancy tests if the site is not able to perform urine testing. A patient who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study.

Peripheral Blood Flow Cytometry for Circulating Tumor Cells

Patients in cohort 3 with Sèzary syndrome have circulating tumor cells; changes in these cells are part of the ISCL/EORTC response assessment criteria (Olsen et al 2011). Testing of Sèzary cell burden is considered part of the standard of care of assessment for this disease. Sèzary cells are defined as either CD4+CD7- or CD4+CD26-. Circulating Sèzary cell (CSC) burden will be initially assessed at screening.

Patients with positive CSC testing at screening, or those with measurable disease at baseline by CT regardless of screening CSC test result will continue to have CSC testing at Week 12, every 12 weeks until Week 96, then every 24 weeks for an additional 96 weeks, then yearly thereafter.

If progression is suspected at Week 12, an additional CSC test will be performed at Week 16 to rule in or out a tumor flare. Patients who meet the criteria for CSC testing at baseline with suspected progression after Week 12 should have CSC testing performed to confirm progression, even if not at a scheduled response assessment timepoint. Patients with assessment of CR, PR, PD, or at end of treatment will have repeat CSC testing. CSC testing will be performed locally.

5.6. Pharmacokinetic Blood Sampling

Blood samples to assess serum tislelizumab concentrations will be collected in patients in both cohorts. Predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9 and 17; 2 postdose (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of Cycles 1 and 5. Postdose PK samples should be collected from a different site than the intravenous site. An additional PK sample is required to be collected at the Safety Follow-Up visit. Should a patient present with any immune-related AE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.

Blood will be collected at the timepoints specified above. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database. Details concerning handling of the PK samples, including processing procedure labeling and shipping instructions will be provided in the laboratory manual for this study.

Samples will be shipped to the designated bioanalytical laboratory for quantification of serum tislelizumab concentrations using a validated method.

Shipping, storage, and handling of samples for the assessment of tislelizumab PK and antidrug antibodies (ADA) assays (Section 5.7) will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

The following assessments will be performed at a central laboratory:

- PK assay: Serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay.
- ADA assays: Serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay.

5.7. Antidrug Antibody Evaluation Procedures

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored.

Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study (Appendix 11).

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

5.8. Unscheduled Visits

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

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

5.9. End of Treatment

The treatment period starts with the first day of assigned study treatment and includes ongoing assessments for safety and efficacy per the Schedule of Assessments in Appendix 11 following completion of protocol-specified treatment. The treatment period ends on the first day of next line therapy or on the day of confirmed disease progression, whichever occurs first.

Section 5.12.1 describes the circumstances where patients may discontinue study drug.

5.10. Safety Follow-up Visit

Patients will return approximately 30 days after the last dose of study drug for a Safety Follow-up visit to collect AEs or SAEs that may have occurred after the patient discontinued from the study treatment. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab. Additionally, outside of the Safety Follow-up visit, all AEs and SAEs, regardless of relationship to study drug, will be reported until 90 days after last dose of study treatment.

Beyond 90 days after treatment discontinuation, all drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, or lost to follow-up, whichever occurs first.

The investigator or his/her designee will also continue to collect information on new anticancer therapy given after the last dose of study drug. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drug. If the patient is unable to return to the clinic and no laboratory assessment is necessary, the investigator or his/her designee will contact the patient or guardian to collect this information.

Any treatment visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up visit. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 5.4.1.

See the study assessments to be performed at the Safety Follow-up visit in Appendix 11. Safety assessments do not need to be repeated if performed within 1 month of the Safety Follow-up visit.

5.11. Long-Term Follow-up

Following discontinuation of the study treatment, all patients will be followed for survival status and study drug-related SAEs, beginning approximately 12 weeks after the Safety Follow-up visit or as directed by the sponsor.

Those patients who discontinue study drug for reasons other than radiographically confirmed disease progression will continue to undergo tumor assessments according to Section 5.4.1 and the Schedule of Assessments (Appendix 11), until radiographically confirmed disease progression.

For all patients in long-term follow-up with disease progression, information on survival follow-up and the subsequent anticancer treatment will be collected via telephone calls, patient medical records, publicly available information and registries, and/or clinic visits approximately every 12 weeks until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

If the patient refuses to return for these visits or is unable to do so, every reasonable effort should be made to contact them or patient's guardian by telephone to determine the patient's disease status and survival.

5.12. Patient, Treatment, Study, and Site Discontinuation

Patients who discontinue study treatment early, but who have not withdrawn consent for follow-up, should be followed for assessments of antitumor activity (Section 5.4.1), safety (Section 5.10), and long-term survival (Section 5.11), if possible.

5.12.1. Treatment Discontinuation

Patients have the right to voluntarily withdraw from the study or discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Reasons that a patient may be discontinued from the study treatment may include, but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety, if he or she were to continue in the study
- Investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance

Every reasonable effort should be made to obtain information on patients who discontinue from study treatment. The primary reason for discontinuation should be documented on the appropriate eCRF.

Patients must discontinue study treatment if they experience any of the following:

- Symptomatic deterioration (eg, uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression
- Intolerable toxicity related to tislelizumab, including development of an immune-mediated AEs determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol anticancer therapy (Section 7.2.2)
- Pregnancy

The primary reason for study drug discontinuation will be documented in the medical chart and on the appropriate eCRF. Patients who discontinue study drug prior to disease progression will not be replaced.

5.12.2. Study Termination and Study Site Closure

Study termination is defined as the time point when data collection will stop. The study will continue until the last patient has died, becomes lost to follow-up, or withdraws from study, or until sponsor decides to terminate the study.

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

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

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

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

Patients receiving tislelizumab, who in the opinion of the investigator, continue to benefit from tislelizumab at study termination, may continue treatment after discussion and agreement by the sponsor. For patients who continue treatment after study termination, these patients will remain on protocol-defined safety and efficacy assessments until completion of the required follow-up schedule. Adverse events and SAEs will be monitored and reported.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate, untimely, or incomplete data recording
- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, all patients have completed all study related assessments and all obligations have been fulfilled)

5.13. Lost to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow-up during the study to complete study related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

If these efforts fail to establish contact, the patient will be considered lost to follow-up.

6. STUDY TREATMENT

6.1. Study Treatment Preparation and Dispensation

6.1.1. Packaging and Labeling

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

6.1.2. Handling and Storage

The study drug 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. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledgment receipt of all study drug shipments. All study drug 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 study drug-specific requirements.

Tislelizumab should be stored at temperatures between 2°C to 8°C (36°F to 46°F) and protected from light. During preparation and delivery of injectable solution to patients, regular room temperature and lighting are tolerable to the drug.

Study drug must be dispensed or administered according to procedures described in the Pharmacy Manual. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug.

6.1.3. Compliance and Accountability

The investigational medicinal product required for completion of this study (tislelizumab) will be provided by the sponsor. The investigational site will acknowledge receipt of investigational medicinal product. Any damaged shipments will be replaced.

Accurate records of all investigational medicinal product received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of investigational medicinal product management.

Patient compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient.

The investigator and/or study personnel will keep accurate records of drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for tislelizumab reconciliation and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain tislelizumab accountability records throughout the course of the study. This person will document the amount of tislelizumab received from the sponsor, the amount supplied, and/or administered to patients, if applicable.

6.1.4. 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 can be destroyed on site or at the depot according to institutional policies, after receiving written sponsor approval.

6.2. Dosage and Administration

Patients will receive tislelizumab at 200 mg intravenously every 3 weeks. One cycle is 21 days. The minimum amount of time between doses is 10 days. If a patient experiences an infusion reaction, he/she may receive pre-medications on subsequent dosing days. The pre-medications should be chosen per institutional standard of care, at the discretion of the treating physician.

The dosing schedule for both cohorts will be the same. The first dose of study drug is to be administered within 5 days after screening assessments have been completed and study eligibility has been determined. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory assessment and AE criteria, as described in Section 6.5.1.

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

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes. If this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

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, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for treatment interruption or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Sections 8.8.9 and 8.9.1, respectively.

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

6.3. Overdose

Any overdose or incorrect administration of study drug should be noted on the study drug administration eCRF. Adverse events associated with an overdose or incorrect administration of study drug will be recorded on the adverse event eCRF. If an overdose or incorrect administration of study treatment takes place, the sponsor is required to be immediately notified.

6.4. Precautions

6.4.1. Surgery and Procedures

With the exception of diagnostic biopsy of tumor tissue or placement of a venous access device, the investigator should discuss with the sponsor medical monitor any patient who requires surgery during the study.

6.5. Dose Interruption, Modification, or Delays

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

6.5.1. Dose Modification for Tislelizumab

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

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

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (refer to the visit window in Appendix 11), with subsequent dosing rescheduled according to the planned schedule every 3 weeks from Cycle 1 Day 1.

Management guidelines for irAEs and infusion-related reactions in patients treated with tislelizumab are presented in Sections 8.8.9 and 8.9.1, respectively.

7. PRIOR AND CONCOMITANT THERAPY

7.1. Prior Therapy

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

7.2. Concomitant Therapy

7.2.1. Permitted Therapy

Most concomitant medications and therapies deemed necessary in keeping with the local standards of medical care at the discretion of the investigator for the supportive care (eg, antiemetics, antidiarrheals) and in a patient's interest are allowed. All concomitant medications will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and intravenous medications and fluids. If changes (dose, stop, or start) in concomitant medication occur during the study, documentation of route, date, and reason for use will be recorded on the eCRF.

All concomitant medications received within 30 days before the first dose of study treatment and 30 days after the last infusion or dose of study treatment should be recorded.

Patients at risk for reactivation of hepatitis B, defined as HBcAb positive, HBsAg negative, and HBV DNA negative at baseline, may continue effective antiviral treatment during screening and throughout the study. It is recommended that antiviral medication start at least 2 weeks before the first dose of tislelizumab and continues until 6 months after the discontinuation of study treatment to decrease the potential risk of viral re-activation. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease guideline because they lack resistance with long-term use (Terrault et al 2016). Antiviral agents with immunomodulatory properties, such as Peg-interferon, are not allowed on study. The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (Appendix 8) and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted. Additionally, patients are permitted to receive treatment with systemic corticosteroids for short durations (< 2 weeks) to treat conditions not associated with the disease under investigation (eg, to treat a flare of chronic obstructive pulmonary disease). Chronic systemic corticosteroid use (≤ 10 mg/day) is permitted – consult the medical monitor for this situation.

Bisphosphonates and RANKL inhibitors (eg, denosumab) are permitted during the trial for a non-malignant indication.

Management guidelines for irAEs and infusion-related reactions in patients treated with tislelizumab are presented in Sections 8.8.9 and 8.9.1, respectively.

7.2.2. Excluded (ie, Prohibited or Restricted) Therapy

7.2.2.1. Therapies Excluded during Tislelizumab Treatment

The following medications are prohibited or restricted at the time of Screening and during the administration of tislelizumab:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE or for short-term use as prophylactic treatment
- Live vaccines within 28 days prior to the first dose of tislelizumab and 60 days following the last dose of tislelizumab
- Herbal remedies with immunostimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, allogeneic stem cell transplantation, topical agents, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer)
- Extensive radiation therapy (except for local, palliative radiotherapy to bone as determined after discussion with the medical monitor)
- Antiviral agents with immunomodulatory properties such as Peg-interferon

The following guidelines should be also followed during the study:

- With the exception of diagnostic biopsy of tumor tissue or placement of a venous access device, the investigator should discuss with the sponsor medical monitor any patient who requires surgery during the study
- Patients should not abuse alcohol or other addictive drugs during the study

8. SAFETY MONITORING AND REPORTING

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

8.1. Safety Overview

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc.) and other assessments. Blood samples will be drawn for determination of ADAs to tislelizumab in patients.

Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available. All AEs and SAEs will be recorded during the trial (AEs from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 90 days after the last dose of study treatment. At the end of treatment, ongoing AEs will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE. Beyond 90 days after treatment discontinuation, all drug-related SAEs will be recorded by investigator until patient death, or lost to follow-up, whichever occurs first.

Investigators are instructed to report all events (including AEs and pregnancy-related AEs). The potential safety issues anticipated in this trial, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections. An IDMC will periodically monitor safety data (Section 11.2).

8.2. Risks Associated with Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Table 7.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested work-up procedures for suspected irAEs are provided in Appendix 8.

8.3. General Plan to Manage Safety Concerns

8.3.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, and patients who have received a live viral vaccine within 4 weeks before the first dose of study drug, are excluded from the study.

8.3.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 11. Clinical laboratory results must be reviewed by the investigator prior to the start of each cycle. An independent data monitoring committee (IDMC) will periodically monitor safety data.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, chemistry, etc.) and other assessments (see Appendix 11 for the Schedule of Assessments). In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to tislelizumab in all patients. All AEs and SAEs will be recorded during the trial (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 90 days after the last dose of study treatment. At the end of treatment, ongoing AEs will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

Immune-related AEs will be recorded up to 90 days after the last dose of tislelizumab. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, or lost to follow-up, whichever occurs first.

Investigators are instructed to report all events (including AEs and pregnancy-related AEs). Reporting requirements for SAEs are discussed in Section 8.7.3. In addition, the sponsor medical monitor or safety physician will review and evaluate observed AEs on a regular basis.

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

Patients who discontinue treatment for any reason will be asked to return to the clinic for a Safety Follow-up visit approximately 30 days after the last study treatment. In addition, telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60 and 90 days (±14 days) after the last dose of tislelizumab.

8.4. Adverse Events

8.4.1. Definitions and Reporting

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

Examples of AEs include:

- Worsening of a chronic or intermittent 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 (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

8.4.1.1. 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 8.4.

8.4.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the tislelizumab Investigator’s Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes assessment of causality for every SAE prior to transmission of the SAE report 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 follow-up information, amending the SAE report accordingly.

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

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

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

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

8.4.1.3. Following Adverse Events

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

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

At the end of treatment, ongoing AEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

New or updated information should be reported to the sponsor according to the SAE instructions outlined in Section 8.7.3.

8.4.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, CBC, coagulation, thyroid function, liver function, or pancreatic enzyme) or other abnormal assessments (eg, electrocardiograms, 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 8.4.1) or an SAE (as defined in Section 8.5). This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present and significantly worsen during the study. The definition of clinically significant is left to the judgement of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- Are associated with clinical signs or symptoms, or
- Require active medical intervention, or
- Lead to dose interruption or discontinuation, or
- Require close observation, or more frequent follow-up assessments, or
- Require further diagnostic investigation

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C reactivation, see Section 5.5.

8.5. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, 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 patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

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

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

The following are NOT considered SAEs:

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

8.6. Suspected Unexpected Serious Adverse Reaction

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

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

8.7.1. Adverse Event Reporting Period

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

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

8.7.2. Eliciting Adverse Events

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

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

8.7.3. Reporting Serious Adverse Events

8.7.3.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form or Pregnancy form

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

8.7.3.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.7.3.1. The SAE Report will

always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality at the time of the initial report as described in Section 8.4.1.2.

The sponsor will provide contact information for SAE receipt.

8.7.3.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.7.3.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

All suspected unexpected serious adverse reactions (as defined in Section 8.6), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

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

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

8.8.1. Recording Diagnosis Versus Signs and Symptoms

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

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

8.8.2. Recording Adverse Events Occurring Secondary to Other Events

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

8.8.3. Recording Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If an AE worsens in grade, the worst grade should be recorded for the entire event.

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

8.8.4. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of "disease progression". If a patient experienced a fatal multi-organ failure due to disease progression, the term "multi-organ failure" should be reported as the SAE, with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression."

8.8.5. Deaths

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

8.8.6. Pregnancies

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

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

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

8.8.7. Recording Post-Study Adverse Events

A post-study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.7.1.

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

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

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

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

- Tislelizumab Investigator's Brochure

8.8.9. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 8.9.3) 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 8.9.3, Table 7. 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.

8.9. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 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.

8.9.1. Infusion-Related Reactions

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for such reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 6.

Table 6: Treatment Modification Guidelines 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.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

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

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

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 (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an antipyretic (eg, paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

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

8.9.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (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 hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and the intensive care unit should be alerted for possible transfer if needed.

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

Tumor Lysis Syndrome

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

Cytokine Release Syndrome

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

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

Patients should be managed appropriately according to local institutional standard of care. Recommended treatment for CRS typically includes high-dose corticosteroids, use of the IL-6 inhibitor tocilizumab, and intense supportive care. A thorough benefit-risk evaluation should be made by the investigator on the

possibility of re-challenge with study treatment for patients who experience severe CRS and subsequently recover. Although there have been anecdotal reports of response to PD-1 inhibitors after re-challenge in ENKL patients with drug-induced CRS, the decision to resume study treatment should be weighed against a variety of factors and may involve consultation with additional specialists and also informing the sponsor's medical monitor.

8.9.3. Immune-Related Adverse Events

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

A list of potential irAEs is shown below in Table 7. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on European Society for Medical Oncology guideline (Haanen et al 2017) and the American Society of Clinical Oncology (ASCO) guideline (Brahmer et al 2018). Common immune-related toxicities are detailed in Appendix 8. For any AEs not included in Appendix 8, please refer to the ASCO Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 7: 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, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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

Management for irAEs is detailed in Appendix 8.

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

9. STATISTICAL METHODS AND ANALYSIS PLAN

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

9.1. Endpoints

9.1.1. Primary Endpoint

The primary endpoint is overall response rate as determined by investigator. Overall response rate is defined as the proportion of patients achieving a best overall response of complete response or partial response. Efficacy will be assessed every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression.

- For cohorts 1 and 2, overall response rate will be measured using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016).
- For cohort 3, overall response rate will be measured using the ISCL/EORTC guidelines (Olsen et al 2011).

9.1.2. Secondary Endpoints

For cohorts 1 and 2, efficacy measures will be determined using the Lugano criteria (Cheson et al 2014) with LYRIC modification for immunomodulatory drugs (Cheson et al 2016). For cohort 3, efficacy measures will be determined using the ISCL/EORTC guidelines (Olsen et al 2011). All measures will be assessed by the investigator.

- Duration of response defined as the time from the first determination of an objective response until progression or death, whichever occurs first, for all cohorts
- Progression-free survival defined as the time from first study drug administration to the date of disease progression or death, whichever occurs first, for all cohorts
- Overall survival, defined as the time from first study drug administration to the date of death due to any reason, for cohorts 1 and 2
- Rate of complete response or complete metabolic response defined as the proportion of patients who achieve complete response or complete metabolic response as best overall response, for all cohorts
- Time to response defined as the time from first study drug administration to the time the response criteria (complete response or partial response) are first met, for all cohorts
- Patient-reported outcomes measured by EORTC QLQ-C30 and EQ-5D-5L questionnaires for all cohorts
- Safety parameters, including AEs, SAEs, clinical laboratory tests, physical exams, and vital signs for all cohorts

9.1.3. Exploratory Endpoints

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

9.2. Statistical Analysis

9.2.1. Analysis Sets

The primary analysis set for both efficacy and safety analyses will be the Safety analysis set (all patients who received at least one dose of study medication).

The PK analysis set includes all tislelizumab-treated patients for whom at least one PK sample is collected according to the protocol and the laboratory manual.

9.2.2. Efficacy Analyses

All efficacy analyses will be performed for each cohort and for the subtypes in cohorts 2 and 3.

9.2.2.1. Primary Efficacy Analyses

Overall Response Rate

Two-sided Clopper-Pearson 95% confidence interval (CI) of ORR in each cohort will be constructed to assess the precision of the point estimate of ORR.

Best overall response is defined as the best response recorded from the start of tislelizumab to the end of the best response determination period. Patients with no post-baseline response assessment will be considered non-responders. The proportion for each response category (CR, PR, SD, and progressive disease) will be presented.

The primary efficacy analysis for each cohort will be conducted when mature response rate data have been observed, estimated as no later than 12 months after the last patient in each cohort received the first dose of study drug.

Additional analysis details will be provided in the SAP.

9.2.2.2. Secondary Efficacy Analyses

Duration of Response

Duration of response will be analyzed using the same methods as PFS and OS, but only summarized for patients who have achieved an overall response. The distribution of duration of response will be summarized by the Kaplan-Meier method.

Progression-free Survival

The median and other quartiles of PFS will be estimated by the Kaplan-Meier method. The 2-sided 95% CIs of median and other quartiles will be constructed using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982). Event-free rates at selected timepoints for PFS will be estimated using the Kaplan-Meier method with their 2-sided 95% CIs based on the Greenwood formula (Kalbfleisch and Prentice 1980).

Data for patients without disease progression or death at the time of analysis will be censored at the time of the last valid tumor assessment. Data for patients who start to receive new anticancer therapy or are

lost to follow-up will be censored at the last valid tumor assessment date prior to the introduction of new therapy or lost to follow-up. More details will be provided in the SAP.

Overall Survival (Cohorts 1 and 2)

Overall survival will be determined using the same methods employed for the PFS analysis.

Complete Response/Complete Metabolic Response

CR rate and complete metabolic response rate will be calculated as the proportion of patients whose best overall response is CR or complete metabolic response, respectively. Complete response rate will be analyzed using the same methods applied for the ORR analysis.

Time-to-Response

Time-to-response will be summarized only for responders by sample mean, median, range, and standard deviation.

Patient-Reported Outcomes

The EORTC QLQ-C30 questionnaire will be summarized for each assessment timepoint. The change from baseline in 'global health status/quality of life' and functional domains (physical functioning, role function, emotional functioning, cognitive functioning and social functioning) will be summarized descriptively.

The scores and their changes from baseline in EQ-5D-5L will be summarized descriptively.

9.2.2.3. Exploratory Efficacy Analyses

[redacted]

9.2.3. Pharmacokinetic Analyses

Pharmacokinetic samples will be collected in this study as outlined in Appendix 11.

Tislelizumab postdose and trough serum concentration data (C_{trough}) will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.2.4. Safety Analyses

The Safety analysis set (all patients who received any dose of study medication) will be used for all safety analyses. All safety analyses will be performed for each cohort and combined.

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v4.03. Laboratory values (eg, hematology, clinical chemistry), vital signs, ECGs, and physical examinations, will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety analysis set.

9.2.4.1. Extent of Exposure

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

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation due to AEs will be summarized. Frequency of the drug discontinuation will be summarized by category.

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

9.2.4.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. Adverse events will be coded to MedDRA (Version 20.0 or higher) lower level term, preferred term and primary system organ class (SOC).

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of a new anticancer therapy. TEAEs also include all irAEs and drug-related serious AEs recorded up to 90 days after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings. The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v4.03 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

9.2.4.3. Clinical Laboratory Analyses

CBC and serum chemistry values will be evaluated for each laboratory parameter by cohort. 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. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI-CTCAE v.4.03 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.2.4.4. Vital Signs Analyses

Descriptive statistics for vital sign parameters (eg, systolic and diastolic BP, heart rate, temperature) and changes from baseline will be presented by visit. Vital signs will be listed by patient and visit.

9.2.4.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.2.4.6. Electrocardiogram

ECG assessments will be performed at the screening visit. Descriptive statistics for baseline ECG parameters will be presented.

9.2.5. Other Analyses

The number of patients enrolled, treated, discontinued from study drug and/or study and those with major protocol deviations will be counted.

Demographic and other baseline characteristics will be summarized in the Safety analysis set using descriptive statistics.

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

9.2.5.1. Prior and Concomitant Therapies

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

9.2.5.2. Immunogenicity Analyses

Samples to assess anti-tislelizumab antibodies will be collected.

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

9.3. Determination of Sample Size

The sample size is based on the precision of the estimates of the ORR. For all cohorts, estimates of the exact 95% CI of the observed ORR for several potential outcomes under assumed cohort/subtype sample sizes are provided in the tables below:

Table 8: Estimates of the Exact 95% CI of the Observed ORR

For a Sample Size of 10:

Sample Size	Observed Responses	ORR	95% CI	
10	2	20%	2.52%	55.61%
10	3	30%	6.67%	65.25%
10	4	40%	12.16%	73.76%
10	5	50%	18.71%	81.29%
10	6	60%	26.24%	87.84%

For a Sample Size of 20:

Sample Size	Observed Responses	ORR	95% CI	
20	4	20%	5.73%	43.66%
20	6	30%	11.89%	54.28%
20	8	40%	19.12%	63.95%
20	10	50%	27.20%	72.80%
20	12	60%	36.05%	80.88%

For a Sample Size of 50:

Sample Size	Observed Responses	ORR	95% CI	
50	10	20%	10.03%	33.72%
50	15	30%	17.86%	44.61%
50	20	40%	26.41%	54.82%
50	25	50%	35.53%	64.47%
50	30	60%	45.18%	73.59%

For a Sample Size of 70:

Sample Size	Observed Responses	ORR	95% CI	
70	14	20%	11.39%	31.27%
70	21	30%	19.62%	42.13%
70	28	40%	28.47%	52.41%
70	35	50%	37.80%	62.20%
70	42	60%	47.59%	71.53%

9.4. Interim Analyses

There is no formal interim analysis planned for this study.

Enrollment will be held if no confirmed tumor responses are seen in the first 10 evaluable patients for cohort 1 and in the first 10 evaluable patients for cohort 2 for subtypes of PTCL-NOS and ALCL, respectively, until the study Steering Committee can meet with the sponsor to discuss the risk/benefit ratio and make a joint decision to determine whether the study enrollment will be permanently discontinued in cohort 1 or subtype(s), based on the overall available data.

If there is only one single confirmed tumor response among the first 10 evaluable patients for cohort 1 or cohort 2 subtypes of PTCL-NOS and ALCL, respectively, the Study Steering Committee and sponsor may also meet to discuss the risk/benefit ratio and determine whether it is appropriate to resume enrollment. If more than one confirmed tumor response is seen in the first 10 patients enrolled in cohort 1 or subtype(s), then enrollment of patients may resume.

9.5. Final Analysis

A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the SAP.

10. DATA HANDLING AND QUALITY ASSURANCE

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

10.1. Data Collection

Data required by the protocol will be entered into the eCRFs in an EDC system that is compliant with all regulatory requirements.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines (eCCGs). The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Form FDA 1572 must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

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

10.2. Data Management/Coding

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

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

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

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

Adverse events and concomitant diseases/medical history will be coded using MedDRA Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

10.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct quality assurance audits. Regulatory agencies may also conduct regulatory inspections 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.

11. STUDY COMMITTEES AND COMMUNICATION

11.1. Steering Committee

This study will be overseen by a Steering Committee consisting of experts in mature T-cell and NK-cell neoplasms and members of the sponsor's staff. The Steering Committee plays a central role in the design of the study, oversees the conduct of the study, and is to agree on a plan for communication of the results.

11.2. Independent Data Monitoring Committee

An IDMC consisting of experts in NK-/T-cell lymphomas, clinical trial safety monitoring, and statistics will evaluate safety data periodically for this study. Approximately every 6 months after the first patient is enrolled, the IDMC will review all available safety data. A separate charter will outline the details for the composition and responsibility of the IDMC.

11.3. Provision of Study Results and Information to Investigators

When the Clinical Study Report is completed, the sponsor will provide the major findings of the study to the investigator.

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

12. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1. Regulatory Authority Approval

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

12.2. Ethical Standard

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

12.3. Institutional Review Board/Independent Ethics Committee

This protocol, the informed consent forms (ICFs), any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

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

12.4. Investigator Responsibilities

12.4.1. 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. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

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 patient has completed the protocol-defined activities.

12.4.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted by the principal investigator and study center in accordance with GCP and all applicable regulatory requirements, including, where applicable, the 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 patients (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. 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 or its authorized representative 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 patients.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients 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 new patients can consent 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.

12.4.3. Informed Consent

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

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

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

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

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

12.4.4. Investigator Reporting Requirements

As indicated in Section 8.7.3.3, 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.

12.4.5. Confidentiality

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the informed consent form process, either as part of the informed consent form or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials

(if allowed) and an identification code (ie, 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 patients screened and for all patients enrolled in the trial.

The investigator agrees that all information received from BeiGene, including but not limited to the Investigator's Brochure, this protocol, CRFs, the investigational 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.

12.4.6. Case Report Forms

For each patient assigned to treatment, an eCRF must be completed and signed by the principal investigator or sub-investigator within a reasonable time period after data collection. If a patient withdraws from the study, the reason must be noted in the appropriate eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRF exists within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRF is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data from that site (eg, paper, CD, or other appropriate media) for archiving the data at the study site.

12.4.7. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction 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.

12.4.8. Inspections

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

12.4.9. Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

12.5. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model informed consent form in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented.

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

12.6. 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.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors or stricter local criteria (International Committee of Medical Journal Editors 2016).

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

12.7. 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
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)

- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

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 noncompliance. 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.

12.8. Records Retention and Study Files

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

The investigator's study file will contain the protocol/amendments, 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.

Patient 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: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, electrocardiogram, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening, and enrollment log, etc.

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

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

Biological samples remaining after this study may be retained in storage by the sponsor for the shorter of a period of up to 2 years or as allowed by the IRB/IEC.

12.9. 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 patient'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 patient's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information 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 patient
- Study results which may be published as described in Section 12.6.

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.

12.10. Joint Investigator/Sponsor Responsibilities

12.10.1. 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 patient records needed to verify the entries on the CRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.10.2. Access to Information for Auditing or Inspections

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

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14. APPENDICES

APPENDIX 1 SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 2, Open-Label Study of BGB-A317 in Patients with Relapsed or Refractory Mature T- and NK-cell Neoplasms

PROTOCOL NO: BGB-A317-207

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

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene, Ltd. at 2955 Campus Drive, Suite 200, San Mateo, CA 94403, United States

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 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 (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	
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
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Response and Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease < 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 2-fluoro-2-deoxy-D-glucose(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: •

Individual target nodes/nodal masses
Extra-nodal lesions
	Score 4 or 5† with an increase in intensity of uptake from baseline and/or
	New FDG-avid foci consistent with lymphoma at interim or end of treatment assessment
		An individual node/lesion must be abnormal with:
		• LDi > 1.5 cm and
		• Increase by ≥ 50% from PPD nadir and
		• An increase in LDi or SDi from nadir
		  ○ 0.5 cm for lesions ≤ 2 cm
		  ○ 1.0 cm for lesions > 2 cm
		• In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline
		• New or recurrent splenomegaly

Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node > 1.5 cm in any axis • A new extra-nodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Cheson et al 2014.

*A score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-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 (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extra-nodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extra-nodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

[†]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

[††]Splenomegaly defined as vertical spleen length > 13 cm.

APPENDIX 3 PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the sponsor medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

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

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

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner is considered highly effective form of birth control only under the following preconditions:

  -Vasectomized partner is the sole sexual partner of the WOCBP trial participant

  -Vasectomized partner has received medical assessment of surgical success.

  - NOTE: Sterile males are those for whom azoospermia, in a semen sample examination, has been demonstrated as definitive evidence of infertility.

    Males with 'low sperm counts' (consistent with 'sub-fertility') are not to be considered sterile for purposes of this study.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).

  - NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

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

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

APPENDIX 5 NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.

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

APPENDIX 6 EUROPEAN QUALITY OF LIFE 5-DIMENSIONS 5-LEVELS HEALTH QUESTIONNAIRE

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

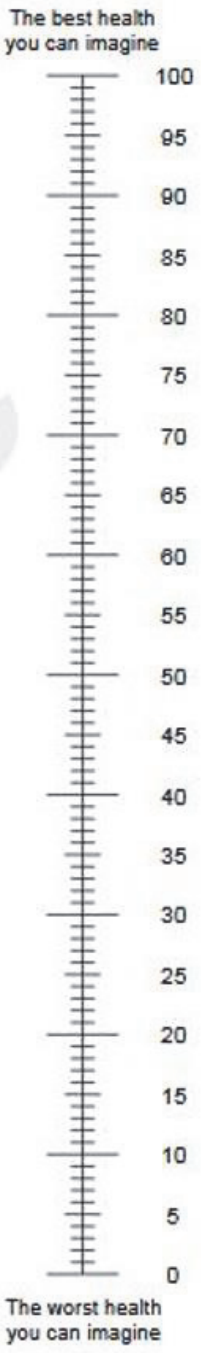
ANXIETY / DEPRESSION

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

2

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

YOUR HEALTH TODAY = ☐



APPENDIX 7 EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER QUALITY OF LIFE CANCER QUESTIONNAIRE QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ⌊⌊⌊⌊⌋

Your birthdate (Day, Month, Year): ⌊⌊⌋⌊⌊⌋⌊⌊⌊⌋

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX 8 IMMUNE-RELATED ADVERSE EVENT 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.

Immune-Related Toxicity	**Diagnostic Evaluation Guideline**
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision or other visual disturbances refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if grade 3-4; every 2-3 days if grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status, and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Immune-Related Toxicity	Diagnostic Evaluation Guideline
Primary adrenal insufficiency	Evaluate ACTH (AM), cortisol level (AM), basic metabolic panel (sodium, potassium, carbon dioxide, glucose). Consider ACTH stimulation test for indeterminate results. If primary adrenal insufficiency (high ACTH, low cortisol) is found biochemically: • Evaluate for precipitating cause of crisis such as infection • Perform an adrenal CT for metastasis/hemorrhage

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

Treatment of Immune-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, re-challenge 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	Continue study treatment or withhold treatment in cases with systemic symptoms.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		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.	
	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-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes	Monitor symptoms every 2-3 days.	Consider holding study treatment until appearance improves and cause is

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		cyclosporine if no response within 72 - 96 hours.	
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If grade 1 persists for > 14 days manage as a grade 2 event	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	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.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		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.	
	3 Rash covers > 30% BSA or grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: • For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. • For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral	Hold study treatment, treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	
	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		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks.	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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		Repeat creatinine/U&E every 48-72 hours.	
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue Study Treatment.
	2 Fasting glucose value 160 - 250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue Study Treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9 – 27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue Study Treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue Study Treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks	Discontinue study treatment
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes	Continue study treatment
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to grade 2, and taper over at least 4 weeks	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	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	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and	Hold study treatment unless improved to grade 0-1; reintroduce only after discussion with the study

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	activity limited	taper over at least 4 weeks.	medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline	Continue study treatment
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a grade 3 event.	Continue study treatment
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to grade 2 and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection	Discontinue study treatment
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as grade 2	Continue study treatment
	2 Moderate weakness with/without pain	If CK is 3X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to grade 0-1. Discontinue if any evidence of myocardial involvement.
Myocarditis	**1** Asymptomatic but	Initiate cardiac evaluation under close monitoring with	Hold study treatment. If a diagnosis of myocarditis is

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as grade 2	confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	Follow the same study drug management for grade 1
	3 Severe symptoms with mild exertion		Discontinue study treatment
	4 Life-threatening		Discontinue study treatment
Primary adrenal insufficiency	**1** Asymptomatic or mild symptoms	Endocrine consultation Replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon) May require fludrocortisone (0.1 mg/day) for mineralocorticoid replacement in primary adrenal insufficiency. Titrate dose up or down as symptoms dictate.	Consider holding study treatment until patient is stabilized on replacement hormone
	2 Moderate symptoms, able to perform ADL	Endocrine consultation Initiate outpatient treatment at 2-3 times maintenance (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to	Consider holding study treatment until patient is stabilized on replacement hormone

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		maintenance doses over 5-10 days Maintenance therapy as in grade 1.	
	3-4 Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Endocrine consultation See in clinic or, for after hours, make an emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg [if the diagnosis is not clear and stimulation testing will be needed]) Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge Maintenance therapy as in grade 1	Hold study treatment until patient is stabilized on replacement hormone

Abbreviations: ADL, activities of daily living; 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.

APPENDIX 9 COCKCROFT-GAULT FORMULA

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

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

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

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

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

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

a Age in years and weight in kilograms.

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

APPENDIX 10 LYMPHOMA RESPONSE TO IMMUNOMODULATORY THERAPY CRITERIA (LYRIC) CLASSIFICATION CRITERIA

Table 2. Comparison of RECIST, irRC, and Lugano Classification criteria

Criteria	CR	PR	PD
RECIST 1.1	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm Note: the appearance of one or more new lesions is also considered progression.
irRC	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart	≥50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart (as measured bidimensionally)	≥25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart, where Tumor Burden = SPD index lesions + SPD new, measurable lesions
Lugano	PET-CT, score 1, 2, or 3* with or without a residual mass on 5PS† OR on CT, target nodes/nodal masses must regress to ≤1.5 cm in LDi	PET-CT score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. OR On CT ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites	PET-CT 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. OR On CT, an individual node/lesion must be abnormal with: LDi >1.5 cm and increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by ≥2 cm from baseline. New or recurrent splenomegaly New or clear progression of preexisiting nonmeasured lesions Regrowth of previously resolved lesions A new node >1.5 cm in any axis or a new extranodal 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 AND/OR new or recurrent involvement of the bone marrow
LYRIC	Same as Lugano	Same as Lugano	As with Lugano with the following exceptions: IR [a] IR(1): ≥50% increase in SPD in first 12 weeks IR(2): <50% increase in SPD with a. New lesion(s), or b. ≥50% increase in PPD of a lesion or set of lesions at any time during treatment IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD

Source: Cheson et al 2016.

Abbreviations: 5PS, 5-point scale; CR, complete response, CT, computed tomography; FDG, fluorodeoxyglucose; IR, immune response; LDi, longest diameter; PD, progressive disease; PET, positron emission tomography; PPD, product of the perpendicular diameters; PR, partial response; SDi, short diameter; SPD, sum of the product of the diameters.

See footnotes on next page.

*A score of 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 deescalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†PET 5PS: 1, no uptake above background; 2, uptake # mediastinum; 3, uptake. mediastinum but # liver; 4, uptake greater than liver; 5, uptake markedly higher than liver (2-3 times SUVmax in normal liver) and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

[a]Additional information:
In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below:

- In the case of IR1, the comparison should be between the first IR1 and the current SPD, with an increase of ≥ 10% constituting PD. In addition, there should be an increase of ≥ 5 mm (in either dimension) of at least 1 lesion for lesions ≤ 2 cm, and 10 mm for lesions > 2 cm.
- In the case of IR2, the new or growing lesion(s) (unless biopsy proven to be benign) should be added to the target lesion(s), up to a total of no more than 6 total lesions. If the SPD of the newly defined set of target lesions has increased ≥ 50% from their nadir value, the patient should be considered to have PD.
- In the case of IR3, since inflammatory responses may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have PD unless there is evidence of PD by an increase in lesion size or the development of new lesions
- If a patient is assessed as having IR and then true PD at a subsequent time point, the initial IR assessment should be corrected to PD

APPENDIX 11 SCHEDULE OF ASSESSMENTS

Study Period or Visit	Screening	Treatment (1 cycle = 21 days)					Post-Treatment Follow-Up	
Cycle	–	1			2 and Beyond	Every 4 Cycles	Safety Follow-Up[a]	Long-Term Follow-Up[b]
Day	-35 to -1	1	8	15	1	End of cycle	~ 30 days after EOT	~ every 12 weeks
Window (Days)	–	–	± 2	± 2	± 7	± 7	± 7	± 7
Informed consent, screen number[c]	X							
Medical and cancer history	X							
Eligibility authorization packet[d]	X							
Request archival tumor tissue[e]	X							
Tislelizumab infusion[f]		X			X			
Pharmacokinetic sampling[g]		X			X		X	
Antidrug antibody sampling[h]		X			X		X	
Safety Assessments[i]								
Vital signs (temperature, BP, pulse)	X	X	X	X	X		X	
Physical examination[j]	X	X	X	X	X		X	
ECOG performance status	X	X	X	X	X		X	
12-lead electrocardiogram[k]	X						X	
Pulmonary and cardiac function tests[l]	X							
Visual acuity and OCT test[x]	X					X	X	
Concomitant medications review	X	X	X	X	X		X	
AE review[m]	X	X	X	X	X		X	X
Efficacy Assessments								
Disease-related constitutional symptoms	X					X	X	
Exam of liver, spleen and lymph nodes[j]	X					X	X	X
Radiologic imaging (PET-CT or CT)[n]	X					X		X
Bone marrow examination[o]	X							
Circulating EBV DNA[p]	X					X	X	
mSWAT (cohort 3 only)[aa]	X	X				X		X
Peripheral blood flow cytometry (cohort 3 only)[bb]	X					X		X
PRO questionnaires[q]		X				X	X	

Study Period or Visit	Screening	Treatment (1 cycle = 21 days)					Post-Treatment Follow-Up	
Cycle	–	1			2 and Beyond	Every 4 Cycles	Safety Follow-Up[a]	Long-Term Follow-Up[b]
Day	-35 to -1	1	8	15	1	End of cycle	~ 30 days after EOT	~ every 12 weeks
Window (Days)	–	–	± 2	± 2	± 7	± 7	± 7	± 7
Hematology[r], chemistry[s], thyroid function[cc],	X	X	X[cc]	X[cc]	X		X	
Liver function[y]	X	X	X	X	X		X	
Coagulation[t], pancreatic enzymes[t]	X							
Hepatitis B and C testing HIV, HTLV-1, -2 testing [dd]	X[u]				X[v]	X[v]	X[v]	
Pregnancy test (if applicable) [w]	X				X	X		
Creatine kinase (CK), creatine kinase-cardiac muscle isoenzyme (CK-MB)[z]	X	X			X		X	

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CR, complete response; CSC, circulating Sèzary cell; CT, computed tomography; EBV, Epstein Barr virus; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PET, positron emission tomography; PRO, patient-reported outcome; SAE, serious adverse event.

Note:

- If hematology, serum chemistry (excluding CK and CK-MB), and liver function laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug administration. If hematology, serum chemistry, and liver function tests are conducted within 72 hours of study drug administration, they do not have to be repeated on Cycle 1 Day 1.
- Disease response will be assessed every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression

a. Approximately 30 days after permanent treatment discontinuation. Safety assessments do not need to be repeated if performed within 1 month of the Safety Follow-up visit.
b. Visits repeat every 12 weeks until death, withdrawal of consent, lost to follow-up, or study termination by the sponsor, whichever occurs first. Those patients who discontinue study drug for reasons other than radiographically confirmed disease progression will continue to undergo efficacy assessments until radiographically confirmed disease progression.
c. This must occur before any study-specific procedures and may be obtained before the 35-day screening window. Consent must be obtained using the current version of the form approved by the ethics committee.
d. After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete an Eligibility Authorization Packet and email it to the medical monitor or designee to agree to the enrollment in writing. Study site personnel should ensure that a final Eligibility Packet is in the patient's file before proceeding with study procedures.
e. Either approximately 20 stained slides or unstained tissue (FFPE with tumor tissue or unstained FFPE slides), together with a pathology report, are required to be sent to the central laboratory for central confirmation of diagnosis and to assess potential predictive biomarkers. In the absence of available

unstained tissue (block or unstained slides) or stained slides, collection of a fresh tumor biopsy at screening is mandatory for central pathology. Central pathology confirmation is not required prior to enrollment.

f. Tislelizumab at 200 mg will be administered by intravenous infusion. It is recommended to use a volumetric pump through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. A pump may not be required if infusion speed can be controlled through alternative means and consistent with approved institutional procedures. The first infusion must commence within 5 days after screening assessments have been completed and study eligibility has been determined.
g. Procedures for collection of PK samples are described in the Laboratory Manual. Predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9 and 17; 2 postdose (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the Safety Follow-Up visit. Should a patient present with any immune-related AE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.
h. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-Up visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.
i. Safety assessments will be conducted on day 1 of every cycle, unless otherwise specified.
j. Body systems will be assessed per standard of care at the study site and as clinically indicated by symptoms. Assessments will include weight and height (at screening only). Assessment of enlargement of liver, spleen, and lymph nodes is included in the physical examination and will be evaluated at screening, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and thereafter yearly until disease progression, and during safety follow-up and long-term follow-up. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance. For cohort 3, examination of the skin is included in the physical examination.
k. A 12-lead electrocardiogram (ECG) will be performed in at Screening, at Safety Follow-up, and as clinically indicated during the study treatment period. The Screening ECG must be performed in triplicate. All ECG recordings should be performed after the patient has been resting for at least 10 minutes, and a repeat ECG should be performed to confirm findings, if any.
l. Pulmonary function tests will include spirometry and lung diffusion capacity and must be performed within 4 weeks prior to first dose of tislelizumab. Cardiac function will be assessed by either echocardiography (ECHO) or multigated acquisition scan (MUGA) and is required at screening unless performed within 90 days of enrollment, subject to review and agreement by the medical monitor or designee.
m. AEs will be recorded from the time of the first dose and all SAEs will be collected after informed consent has been signed but prior to administration of the study drug. Telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anticancer therapy) at 60, and 90 days (±14 days) after the last dose of tislelizumab. All AEs and SAEs, regardless of relationship to study drug, will be recorded until up to 90 days after the last dose of study treatment, regardless of initiation of new anticancer therapy. Beyond 90 days after treatment discontinuation, all drug-related SAEs will be recorded by investigator until patient death, or lost to follow-up, whichever occurs first.
n. Patients in cohorts 1 and 2 will undergo PET-CT assessment at screening. Patients whose disease is not PET-avid at screening will be followed by CT-based assessments alone. Patients whose disease is PET-avid at screening will be followed by an integration of PET-CT and CT-based assessments (ie, PET-CT assessments will be performed at screening, weeks 24 and 48, and for any of the following: to confirm a result on a CT scan [CR/PR or disease progression] or to confirm or refute true disease progression in patients who are classified as having an IR as a follow-up evaluation within 12 weeks). Tumor assessments, including radiographic imaging, will be performed at screening, at Week 12 from C1D1, every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, and then yearly until disease progression. If there is a concern about early progression, imaging at the end of Cycle 1 to document progression is recommended. CT-based assessments should be of diagnostic quality with contrast administered. MRI may be substituted for CT

only for patients with serious contrast allergy. Patients in cohort 3 will undergo diagnostic-quality PET and/or CT imaging at screening. If patients do not have measurable disease at screening, imaging will only be required for response assessments if progression is suspected by the investigator. Imaging is not required to confirm CR, PR, or SD; if there is lymph node involvement, PET and CT imaging will be conducted while on study. If patients have measurable disease at screening, CT imaging will occur at Week 12 from C1D1, every 12 weeks until week 96, every 24 weeks for an additional 96 weeks, then yearly until disease progression. If progression is seen at Week 12, imaging will be repeated at Week 16 to rule in or out a tumor flare. Imaging should be performed at any time point where disease progression is suspected after Week 12.

o. Bone marrow core biopsy will be required at screening (unless completed within 90 days of enrollment, subject to review and agreement by the medical monitor or designee) to assess bone marrow involvement of lymphoma and to confirm a CR in patients with bone marrow involvement at screening. All pathology samples will be collected and reviewed at investigational sites.
p. Circulating EBV DNA will be quantified with quantitative polymerase chain reaction. Patients in cohort 1 and cohort 2 whose disease is determined to be EBV-negative by EBER ISH at screening are not required to undergo subsequent circulating EBV DNA assessments during screening and study treatment periods.
q. All patients should complete the EQ-5D-5L and EORTC QLQ-C30 questionnaires before the first dose of study drug.
r. Complete blood count and differential will be evaluated by a local laboratory. CBC includes hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell count with differential including neutrophils (including bands, if available), lymphocytes, monocytes, eosinophils, and basophils.
s. Serum chemistry will be evaluated by a local laboratory and includes sodium, potassium, chloride, bicarbonate or CO_2 (or if neither are available, CO_2 combining power) glucose, blood urea nitrogen or serum urea, creatinine, calcium, phosphate/phosphorus, magnesium, total protein, albumin, lactate dehydrogenase, and alkaline phosphatase. Liver function tests include total bilirubin, alkaline phosphatase, ALT, and AST.
t. Coagulation parameters will be tested if clinically indicated while on treatment. Prothrombin time (reported as international normalized ratio) and activated partial thromboplastin time will be evaluated by a local laboratory. Pancreatic enzymes (amylase and lipase) will be tested if clinically indicated while on treatment.
u. Hepatitis B serology includes HBsAg, HBcAb, HBsAb. Patients who are HBsAg negative (required for study eligibility) and HBcAb positive should have HBV DNA testing performed. If HBV DNA is detectable by an assay with a sensitivity of ≤ 20 IU/mL, the patient is not eligible for the study. Hepatitis C testing includes HCV antibody as well as HCV RNA by PCR if the patient is HCV antibody positive; patients with a detectable level of HCV RNA (≥ 15 IU/mL) are not eligible. Sensitivity criteria for performance of HBV DNA and HCV RNA PCR assays are described in Section 5.5.
v. After screening, HBV DNA or HCV RNA testing is required only for patients who are at risk for HBV and/or HCV reactivation. Patients who are HBcAb-positive and HBsAg-negative with undetectable HBV DNA will be monitored regularly by an HBV DNA assay as described in Section 5.5. The interval for HBV DNA testing depends on whether patients are on antiviral prophylaxis as described in Section 5.5. Patients who are HCV antibody-positive, but negative for HCV RNA, will undergo viral load testing (HCV RNA by PCR) as described in Section 5.5. All patients at risk for reactivation will have HBV DNA and/or HCV RNA testing performed at the Safety Follow-up visit.
w. For all women of childbearing potential (including those who have had a tubal ligation), a serum pregnancy test will be performed at screening within 7 days of the first dose of study drug. Urine pregnancy tests will be performed every cycle during the treatment phase of the study. Pregnancy tests must be continued every 3 weeks for at least 120 days after the last dose of study drug. Pregnancy tests will be evaluated by local laboratories. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Serum pregnancy tests may be substituted for urine pregnancy tests if the site is not able to perform urine testing.
x. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 90 days of enrollment (subject to review and agreement by the medical monitor or designee) may be used rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test, including a dilated fundoscopic examination) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 12 weeks for 96 weeks, then every 24

weeks for an additional 96 weeks, and then yearly until the patient discontinues from study treatment. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

y. Liver function tests include ALT, AST, alkaline phosphatase, and total bilirubin, and will be evaluated by a local laboratory. Liver function tests are required weekly during Cycles 1 and 2, with further monitoring if increases are observed in the first 2 cycles, according to Appendix 8.

z. All patients will have CK and CK-MB testing at screening and all scheduled visits during the first 3 treatment cycles, all predose assessments from Cycle 4 onwards, and at the end of treatment and Safety Follow-up visits. In the event that CK-MB fractionation is not able to be evaluated using the local laboratory, please assess troponin I and/or troponin T instead.

aa. For cohort 3 only: Skin assessment by mSWAT will be performed starting at Week 12, then every 12 weeks for 96 weeks, then every 24 weeks for an additional 96 weeks, then yearly thereafter. If progression is suspected at Week 12, an additional response assessment will be performed at Week 16 to rule in or out a tumor skin flare. Patients with suspected progression after Week 12 should have all response assessments performed, even if not at a scheduled response assessment timepoint, to confirm progression.

bb. For cohort 3 only: Circulating Sèzary cell (CSC) burden will be initially assessed at screening. Patients with positive CSC testing at screening, or those with measurable disease at baseline by CT, regardless of screening CSC test result, will continue to have CSC testing at Week 12, every 12 weeks until week 96, then every 24 weeks for an additional 96 weeks, then yearly thereafter. If progression is suspected at Week 12, an additional CSC test will be performed at Week 16 to rule in or out a tumor flare. Patients who meet criteria for CSC testing at baseline with suspected progression after Week 12 should have CSC testing performed even if not at a scheduled response assessment timepoint to confirm progression. Patients with assessment of CR, PR, PD, or at end of treatment will have repeat CSC testing. CSC testing will be performed locally.

cc. Thyroid function tests include free T3, free T4, and TSH. For Cycle 1 Days 8 and 15 only: no thyroid function tests are required.

dd. **For Germany only:** For patients who do not have known HIV/HTLV-1, -2 infection, HIV/HTLV-1,-2 testing will be performed at screening. All patients who test positive at screening will not be eligible for the study.

APPENDIX 12 CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Blood urea nitrogen or urea Creatinine Glucose Lactate dehydrogenase Total protein Potassium Sodium Creatine kinase (CK) Creatine kinase-cardiac muscle isoenzyme (CK-MB)[a]	Hematocrit Hemoglobin Platelet count WBC count Neutrophil count Lymphocyte count	Prothrombin time Activated Partial Thromboplastin Time International Normalized Ratio

Abbreviations: WBC, white blood cell.

Note: Additional laboratory assessments may be conducted if required for clinical management; relevant data from those assessments will be collected by the sponsor.

a. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead

APPENDIX 13 ISCL/EORTC GUIDELINES FOR RESPONSE ASSESSMENT OF MF/SS PATIENTS

Table 1: Response in Skin

Response	Definition
Complete response	100% clearance of skin lesions*
Partial response	50%-99% clearance of skin disease from baseline without new tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease
Stable disease	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T_3) in patients with T_1, T_2, or T_4 only skin disease
Progressive disease†	≥ 25% increase in skin disease from baseline or
	New tumors (T_3) in patients with T_1, T_2 or T_4 only skin disease or
	Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

As published by Olsen et al 2011. Based on modified Severity Weighted Assessment Tool score.
* A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.
† Whichever criterion occurs first.

Table 2: Response in Lymph Nodes*

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of each abnormal lymph node at baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD†	≥ 50% increase in SPD from baseline of lymph nodes or
	Any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or
	Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically

As published by Olsen et al 2011. Based on modified Severity Weighted Assessment Tool score.
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
* Peripheral and central lymph nodes.
† Whichever criterion occurs first.

Table 3: Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen; any post treatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression in any splenic or liver nodules, or in measureable disease (SPD) in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD*	> 50% increase in size (SPD) of any organs involved at baseline or
	New organ involvement or
	Loss of response: > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR
Relapse	New organ involvement in those with CR

As published by Olsen et al 2011. Based on modified Severity Weighted Assessment Tool score.
Abbreviations: CR, complete response; PR, partial response; SPD, sum of the maximum linear dimension (major axis) × longest perpendicular dimension (minor axis); SD, stable disease; PD, progressive disease.
* Whichever criterion occurs first.

Table 4: Response in Blood*

Response	Definition
CR†	B_0
PR‡	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD§	B_0 to B_2 or
	> 50% increase from baseline and at least 5,000 neoplastic cells/μL or
	Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/μL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

As published by Olsen et al 2011. Based on modified Severity Weighted Assessment Tool score.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
* As determined by absolute numbers of neoplastic cells/μL.
† If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
‡ There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
§ Whichever occurs first.

Table 5: Global Response Score

Global Score*	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any		
		SD	CR/NI, PR, SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

As published by Olsen et al 2011. Based on modified Severity Weighted Assessment Tool score.
Abbreviations: CR, complete response; NI, noninvolved; PR, partial response; PD, progressive disease; SD, stable disease.

APPENDIX 14 MODIFIED SEVERITY WEIGHT ASSESSMENT TOOL (MSWAT)

Quantitation of skin involvement and severity by disease in patients in Cohort 3 will be assessed using the modified skin weight assessment tool (mSWAT) (Olsen et al 2007).

The investigator will first assess involvement by disease of each of 12 body regions as defined in the following chart. The chart on the following page defines the approximate percent body surface area for each region.

The extent of smaller lesions in each area are approximated by using the flexor surface of the hand (the palm and fingers) as a "ruler" to measure the body surface area involvement within each region. The flexor surface of the hand, which includes the palm, fingers, thumb, from wrist to fingertips, is approximated to 1% of the total body surface area. The flexor surface of the hand without including the fingers is approximated to 0.5% of the total body surface area.

Each lesion is defined, in rising severity, as a patch, plaque, or tumor.

- **Patch:** abnormal skin without elevation from normal skin, with flat erythema or erythema with mild infiltration
- **Plaque:** abnormal skin elevated from normal skin by <5mm, with elevated erythema or erythema with moderate infiltration
- **Tumor:** abnormal skin elevated from normal skin by ≥5mm, with erythema with fissuring, ulceration, or tumor.

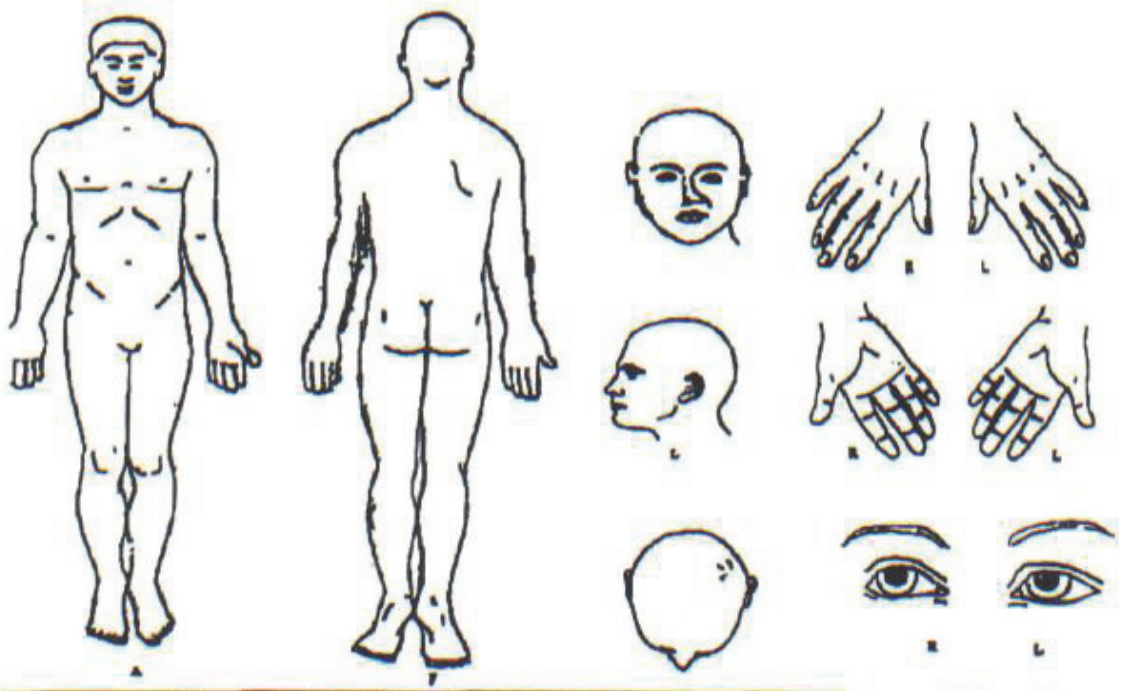
mSWAT score is calculated as follows:

	% BSA Patch	_____	x 1
+	% BSA Plaque	_____	x 2
+	% BSA Tumor	_____	x 4
	mSWAT Score	_____	(max 400)

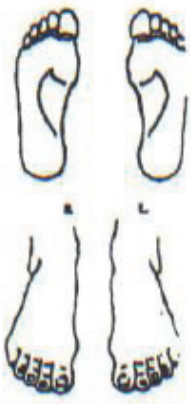
It is recommended that the same investigator at all time points performs mSWAT assessment to eliminate inter-observer variability for a given patient.

Subject # ___ – ____ (site – subject) Initials ___ (F M L) Visit Date ___ (month) ___ (day) ____ (year)

BODY-SURFACE AREA ASSESSMENT



Area	%BSA for region	% BSA Patch	%BSA Plaque	%BSA Tumor
Head	7			
Neck	2			
Anterior Trunk	13			
Posterior Trunk	13			
Buttocks	5			
Genitalia	1			
Upper arms	8			
Forearms	6			
Hands	5			
Thighs	19			
Lower leg	14			
Feet	7			
Total	100			



Total BSA Involvement % BSA Patch _____

% BSA Plaque _____

% BSA Tumor _____

Total BSA Involvment % BSA = _____

APPENDIX 15 MODIFIED ISCL/EORTC REVISIONS TO THE TNMB CLASSIFICATION OF MF/SS

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	One or more tumors (≥ 1 cm diameter)
T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive
B_1	Low blood tumor burden: > 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥ 1,000/μL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

As published by Olsen et al 2011.

* Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: pokiloderma may be present. Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present. Tumor = any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.
† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions to include central nodes. Lymph nodes are qualified as abnormal if > 1.5 cm in diameter.
‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Clinical Staging

Stage	T	N	M	B
IA	1	0	0	0, 1
IB	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

Abbreviations: ISCL, International Society for Cutaneous Lymphomas; EORTC, European Organisation for Research and Treatment of Cancer; MF, mycosis fungoides; SS, Sézary syndrome; X, clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.