Clinical Study Protocol

Protocol Title:	A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer
Protocol Number:	BGB-A317-204
Date of Protocol:	05 August 2020, Version 5.0
Study Phase:	2
Sponsor:	BeiGene (Shanghai) Co., Ltd. 4th Floor, Building D 780 Cailun Road China (Shanghai) Pilot-fee Trade Zone Shanghai, China 201203
Sponsor Medical Monitor:	[redacted]

PROTOCOL APPROVAL SHEET

PROTOCOL TITLE: A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer

PROTOCOL NO: BGB-A317-204

BeiGene Approval:

[redacted]

Medical Monitor

06- Aug- 2020.

Date

INVESTIGATOR SIGNATURE PAGE

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Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name of the center in which the study will be conducted.

I have read the entire protocol and agreed to carry out the study according to this protocol:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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PROTOCOL SYNOPSIS

Name of Sponsor/Company:	**BeiGene (Shanghai) Co., Ltd.**
Name of Finished Product:	**Tislelizumab (BGB-A317) Injection**
Name of Active Ingredient:	**Tislelizumab (BGB-A317)**
Title of Study:	A Single-Arm, Multicenter Phase 2 Study of BGB-A317 in Patients with Previously Treated PD-L1+ Locally Advanced or Metastatic Urothelial Bladder Cancer
Protocol No:	**BGB-A317-204**
Study Centers:	Approximately 30 sites in China and other Asian countries
Study Plan: Screening (up to 28 days), treatment (until disease progression, intolerable toxicity, or withdrawal for other reasons), safety follow-up, and survival follow-up.	**Phase:** 2

Objectives:

Primary:

- To determine the efficacy of tislelizumab (also known as BGB-A317) in patients with previously treated, program death ligand-1 positive (PD-L1+), locally advanced or metastatic urothelial bladder cancer (UBC), as measured by the objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessed by independent review committee (IRC)

Secondary:

- To evaluate the efficacy of tislelizumab as measured by duration of response (DOR), progression-free survival (PFS), and disease control rate (DCR) according to RECIST version 1.1 assessed by IRC
- To evaluate the efficacy of tislelizumab as measured by overall survival (OS)
- To evaluate the efficacy of tislelizumab as measured by ORR, DOR, PFS and DCR according to RECIST version 1.1 and immune-related RECIST (irRECIST) assessed by investigators
- To evaluate the safety and tolerability of tislelizumab as determined by the frequency and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03, and the rate of discontinuation of treatment due to AEs

Exploratory:

- [redacted]

Study Design:

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the anti-programmed cell death-1 (PD-1) monoclonal antibody tislelizumab in participants with PD-L1+, locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen. The study is composed of an initial screening phase (up to 28 days), a treatment phase (until disease progression, intolerable toxicity, or withdrawal for other reasons), safety follow-up phase, and survival follow-up phase.

Approximately 110 patients will be allocated to receive 200 milligram (mg) of tislelizumab intravenously (IV) every 3 weeks. Radiological assessment of tumor-response status should be performed every 9 weeks (±1 week). Tumor response will be assessed by IRC based on the RECIST version 1.1, and by investigators based on RECIST version 1.1 and irRECIST. Pseudo-progression may occur due to immune cell (IC)

infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not to exceed 12 weeks from the initial documentation of PD. The patient must be re-consented and the following criteria must be met in order to continue the treatment after initial PD: a. Absence of clinical symptoms and signs of disease progression (including clinically significant worsening laboratory values). b. Stable Eastern Cooperative Oncology Group (ECOG) performance status. c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention. Patients will be evaluated for AEs (all grades, according to NCI-CTCAE version 4.03), serious adverse events (SAEs), and any AE that leads to treatment discontinuation will be followed up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline or ≤ Grade 1, the investigator assesses the event as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE. Immune-related AEs will be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If a patient discontinues study treatment due to the reasons other than disease progression or death, then tumor assessments should continue to be performed following the scheduled assessment plan until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawn consent.	
Planned number of patient**s:**	Approximately 110 patients
Study Population	**Inclusion criteria**: 1. Patients with histologically or cytologically documented locally advanced (T4b, any N; or any T, N2-3) or metastatic (M1, Stage IV) transitional cell carcinoma (TCC) of the urothelium (including renal pelvis, ureters, urinary bladder, urethra) 2. Disease progression during or following treatment with at least one platinum-containing regimen for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence a. Patients who received prior neoadjuvant or adjuvant chemotherapy and progressed within 12 months of treatment with platinum-containing regimen will be considered as second-line patients b. Patients intolerant to platinum-containing regimen due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible Note: No more than 2 prior lines of systemic therapy for metastatic UBC 3. Patients must submit archival tumor tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or at least 5 unstained slides) with an associated pathology report, or agree to a tumor biopsy for determination of program death ligand-1 (PD-L1) expression and other biomarker analyses (fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies). PD-L1 expression will be assessed centrally, and patients who are tested as PD-L1 high are eligible. PD-L1 expression is defined as high: • If ICs involve >1% of the tumor area, either ≥25% of tumor

	cells (TCs) or ≥25% of ICs express PD-L1 • If ICs involve ≤ 1% of the tumor area, TCs ≥25% or ICs=100% And PD-L1 expression is defined as low/negative if it did not meet the criterion for PD-L1 high. Note: Tumor tissue should be of good quality based on total and viable tumor content. 4. Patients must have at least one measurable lesion as defined per RECIST version 1.1 assessed by the investigator (imaging report must be submitted to the sponsor medical monitor to permit review of measurable disease at baseline) 5. Male or female, aged ≥18 years on day of signing informed consent 6. Patients have voluntarily agreed to participate by giving written informed consent 7. ECOG performance status of ≤1 8. Life expectancy ≥12 weeks 9. Patient must have adequate organ function as indicated by the following screening laboratory values obtained within 7 days prior to the first study treatment a. Absolute neutrophil count (ANC) $\geq 1.5\times10^9$/L b. Platelets $\geq 100\times10^9$/L c. Hemoglobin ≥9 g/dL or ≥5.6 mmol /L (Note: Criteria must be met without a transfusion within 14 days of obtaining the sample) d. Calculated creatinine clearance ≥ 30 milliliter (mL)/min (Cockcroft-Gault formula, see Appendix 5) e. Serum total bilirubin ≤ 1.5 X upper limit of normal (ULN) (total bilirubin must be <4 X ULN for patients with Gilbert's syndrome) f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 X ULN OR ≤ 5 X ULN for patients with liver metastases 10. Female patients are eligible to enter and participate in the study if they are of: a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant), including any female who i) Has had a hysterectomy ii) Has had a bilateral oophorectomy (ovariectomy) iii) Has had a bilateral tubal ligation iv) Is post-menopausal (total cessation of menses for ≥1 year) b. Childbearing potential, has a negative serum pregnancy test at screening (within 7 days before the first investigational product administration), not be breast feeding, and agree to remain abstinent (refrain from heterosexual intercourse) or uses adequate contraceptive methods that result in a failure rate of <1% per year before study entry and throughout the study until 120 days after the last investigational product administration Note: Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit

	ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices. 11. Male patients are eligible to participate in the study if they are vasectomized or agree to use contraception during the study treatment period and for at least 120 days after the last dose of study drug **Exclusion criteria**: 1. History of severe hypersensitivity reactions to other humanized monoclonal antibodies 2. Prior active malignancy within 2 years prior to Cycle 1 Day 1, exceptions include the tumor under investigation in this study, localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse, and locally recurring cancers that have undergone curative intent treatment, such as resected basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast. 3. Prior therapies targeting PD-1 or PD-L1. 4. Active brain or leptomeningeal metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments. Patients with brain metastases are permitted if they are asymptomatic, eg, diagnosed incidentally at screening by brain MRI, or patients with previously treated brain metastases that are asymptomatic, radiographically stable and not requiring steroid medications for at least 4 weeks prior to Cycle 1 Day 1. 5. Patients with active autoimmune diseases or history of autoimmune diseases that may relapse should be excluded (see Appendix 4 for a more comprehensive list of autoimmune diseases). Patients with the following diseases are allowed to be enrolled for further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), controlled celiac disease, or diseases not expected to recur in the absence of external triggering factors. 6. Patients should be excluded if they have conditions requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Note: Adrenal replacement doses ≤ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease; patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted 7. Has history of interstitial lung disease or non-infectious pneumonitis except for those induced by radiation therapies 8. With severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to first dose of study drug. 9. With uncontrollable pleural effusion, pericardial effusion or ascites

	requiring pleurocentesis or abdominal tapping less than 4 weeks 10. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate. 11. Known history of Human Immunodeficiency Virus (HIV) 12. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carrier with HBV deoxyribonucleic acid (DNA) ≥500 IU/mL (or 2.5×10^3 cps/mL), or active hepatitis C should be excluded. Patient with inactive hepatitis B surface antigen (HBsAg) carrier, active HBV infection with sustained anti-HBV suppression (HBV DNA <500 IU/mL or 2.5×10^3 cps/mL) and patients whose hepatitis C has been cured (hepatitis C virus [HCV] ribonucleic acid [RNA] is lower than detection limit) can be enrolled 13. Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs 14. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies (including Chinese herbal medicine and Chinese patent medicines) used to control cancer within 2 weeks of Cycle 1 Day 1. AEs associated with these therapies must be Grade 0-1, baseline or stabilized (except for alopecia) 15. Prior allogeneic stem cell or solid organ transplant 16. Administration of a live or attenuated vaccine within 4 weeks prior to study drug administration 17. Major surgical procedure other than for diagnosis within 28 days prior to study drug administration
Test product, dose and mode of administration:	Tislelizumab, 10 ml/vial, 10 mg/ml. 200 mg every 3 weeks (Q3W) administered by intravenous (IV) infusion
Reference therapy, dose, and mode of administration:	Not applicable

Study Endpoints:

Primary Endpoint:

- ORR – defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by IRC using RECIST version 1.1

Secondary Endpoints:

Efficacy:

- DOR – defined as the time from the first determination of a confirmed objective response by IRC according to RECIST version 1.1 until the first documentation of progression or death, whichever comes first
- PFS – defined as the time from the date of first dose of study drug to the date of first documentation of disease progression assessed by IRC using RECIST version 1.1 or death, whichever occurs first
- DCR – defined as the proportion of patients who achieve CR, PR and stable disease (SD) assessed by IRC using RECIST version 1.1
- OS – defined as the time from the date of first dose of study drug until the date of death from any cause
- ORR, DOR, PFS and DCR assessed by investigators per RECIST version 1.1 and irRECIST respectively

Safety:

To evaluate the safety and tolerability of tislelizumab, as defined by:

- The incidence and severity of AEs according to NCI-CTCAE version 4.03
- Changes in vital signs, physical findings, and clinical laboratory results

Exploratory Endpoints:

[redacted]

Statistical Methods:

Analysis Sets:

The Safety analysis set will include all patients who have received any dose of tislelizumab.

The Efficacy Evaluable analysis set includes all patients who have received any dose of tislelizumab and had measurable disease per IRC according to RECIST version 1.1 at baseline. This will be the primary analysis set for the efficacy analyses.

The Per-Protocol (PP) analysis set includes patients in the Efficacy Evaluable analysis set who had no major protocol deviations. Criteria for exclusion from the PP analysis set will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis set for efficacy analysis when there are over 15% patients, ie, 17 patients, who had major protocol deviations.

Primary Efficacy Analysis:

The primary efficacy endpoint is ORR as determined by IRC using the RECIST version 1.1. ORR is defined as the proportion of patients achieving best overall responses of CR or PR.

The ORR in this study is estimated as 25%, which is deemed a clinical meaningful improvement based on a historical control of 10%. Hence, the null and alternative hypotheses are set as following:

H_0: ORR=10%
H_a: ORR ≥25%

A binomial exact test will be performed for hypothesis testing among the evaluable patients (ie, patients with measurable disease at baseline) in the Efficacy Evaluable analysis set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the single agent tislelizumab statistically significantly increases ORR compared with historical control. Therefore, the superiority of single agent tislelizumab will be demonstrated.

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

The primary efficacy analysis will be conducted no later than 6 months after the first dose of the last patient, and will be based on the Efficacy Evaluable analysis set. In case of patients without measurable disease per IRC who have been enrolled and treated, they will be excluded from the primary efficacy analysis.

Secondary Efficacy Analysis:

DOR will be estimated using the Kaplan-Meier (KM) method. Its 95% CI will be constructed using Greenwood's formula. DOR censoring rule will follow United States Food and Drug Administration (FDA) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007). Only patients who have achieved objective responses will be included in the analysis of DOR.

PFS and OS will be analyzed similarly as DOR in the Efficacy Evaluable analysis set. PFS at 12 months and OS at 12 months will be calculated based on KM method.

DCR will be summarized similarly as ORR in the Efficacy Evaluable analysis set.

Efficacy outcomes based on tumor assessment (ORR, DOR, PFS and DCR) per investigator review according to RECIST version 1.1 and irRECIST, respectively, will be summarized in the secondary efficacy analyses.

Safety Analysis:

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v4.03. Laboratory values (eg, hematology, clinical chemistry, urinalysis), vital signs, electrocardiograms, 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.

Sample Size:

The sample size calculation was based on the power of the comparison between estimated ORR in the study and the historical rate. It is assumed an ORR of 25% in the study as compared to 10% in the historical control. Using a binomial exact text, the power is 0.986 with 110 patients to demonstrate statistical significance at a 1-sided alpha of 0.025.

LIST OF ABBREVIATIONS AND DEFINTIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BGB-A317	Humanized monoclonal antibody directed at PD-1
BOR	Best overall response
C1q	Complement 1q, a subunit of complement 1
CI	Confidence Interval
CK	Creatine kinase
CK-MB	Creatine kinase cardiac muscle isoenzyme
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CSR	Clinical Study Report
CT	Computed tomography
C_{trough}	Minimum observed plasma concentration
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
Fc	Fragment crystallizable region (typically, of immunoglobulin G)
FcγR	Gamma Fc receptor, such as FcγaRI, FcγIRIII, etc.
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
GC	gemcitabine + cisplatin
HBcAb	Antibody against hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HPF	High power field
IB	Investigator's Brochure
IC	Immune Cell

Abbreviation	Definition
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G, such as IgG1, IgG2, IgG3 and IgG4; other types of immunoglobulins include IgM, IgD and etc.
IND	Investigational New Drug
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRC	Independent Review Committee
IRB	Institutional Review Board
irRECIST	immune-related RECIST
IV	Intravenous(ly)
K_D	Dissociation constant
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIBC	Muscle Invasive Bladder Cancer
mL	milliliter
MRI	Magnetic resonance imaging
MVAC	methotrexate + vinblastine + adriamycin + cisplatin
NaF	Sodium fluoride
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NMIBC	Non-Muscle Invasive Bladder Cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Program Death Ligand-1
PD-L1+	Program Death Ligand-1 positive
PD-L2	Program Death Ligand-2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PP	Per-Protocol
PR	Partial response

Abbreviation	Definition
PSA	Prostate-specific antigen
PT	Prothrombin Time
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
SPD	Sum of the products of the two largest perpendicular diameters
TC	Tumor Cell
TCC	Transitional Cell Carcinoma
TEAE	Treatment-Emergent Adverse Event
TIL	Tumor-infiltrating lymphocytes
tislelizumab	BGB-A317
TMTB	Total Measured Tumor Burden
TSH	Thyroid-stimulating hormone
UBC	Urothelial Bladder Cancer
ULN	Upper limit of normal
WBC	White blood cell

1. BACKGROUND

1.1. Background on Bladder Cancer

Urothelial bladder cancer (UBC) is the most common cancer of the urinary system worldwide, with transitional cell carcinoma (TCC) of the bladder being the predominant histologic type and location. Although less common, urothelial cancers may originate in the renal pelvis, ureters, or urethra. It was estimated that in 2016, there would be 76,960 new cases of bladder cancer and 16,390 deaths in the United States (American Cancer Society). Similar worldwide data estimate that there were 123,051 deaths in men and 42,033 in women in 2012 (GLOBOCAN 2012).

In China, bladder cancer is one of the most common urologic malignancies and life-threatening diseases. The occurrence of bladder cancer is correlated with both genetic factors and external factors. Currently tobacco consumption and long-term exposure to chemicals are two leading risk factors. Additional factors such as chronic infections, water pollutions, family disease history, etc. also contribute to the incidence of bladder cancer (Chinese Urological Association [CUA] 2014).

In 2008, the incidence of bladder cancer in all cancer registration areas in China was 7.49/100,000 which is higher than the rate (4.53/100,000) by world standard population. This figure ranked first in male urologic malignancies in China as well as eighth in general. In addition, the incidence of bladder cancer in males is 3.3 times higher than that in female population (Han 2013). In 2015, there were 80,500 new cases of bladder cancer and among them 32,900 deaths were reported (Chen et al 2016).

The majority of urothelial tumors arise in the bladder with the remainder originating in the renal pelvis, urethra, or ureter. TCC is the most common histologic subtype associated with bladder cancer and accounts for greater than 90% of all UBC cases in the industrialized world, whereas non-urothelial subtypes, including squamous cell, adenocarcinoma, and small cell carcinoma, are more frequent in other areas of the world (Immune Related Adverse Reactions Management Guide of Nivolumab). According to the database established by Chinese Bladder Cancer Consortium, from 2007 to 2012, the most common histologic types of bladder cancer were urothelial carcinoma (91.4%), among which non-muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) were 74.1 and 25.2%, respectively (Li 2015).

The overall 5-year survival rate for metastatic UBC is approximately 5.2% (National Cancer Institute). Poor prognostic factors for survival in patients with metastatic UBC include advanced stage of disease at the time of initial diagnosis, Karnofsky performance status < 80%, visceral metastasis (ie, lung, liver, or bone) (Bajorin 1999). The presence of these unfavorable features was associated with a median survival of 4 months compared with 18 months in patients without these features (Loehrer 1992).

1.2. Treatment for Metastatic or Unresectable Urothelial Bladder Cancer

Cisplatin-based chemotherapy combination is the preferred first-line therapy worldwide for patients with metastatic UBC, for example GC (gemcitabine + cisplatin) and DD-MVAC (a modified regimen of methotrexate + vinblastine + adriamycin + cisplatin). Nonetheless, a

significant number of patients are not appropriate candidates for cisplatin-based chemotherapy combinations because of comorbidities and impaired functional status (Dash 2006). For such patients, alternative options such as gemcitabine monotherapy, gemcitabine + paclitaxel, etc. are available (NCCN Guidelines Version 2, 2016: Bladder Cancer Version 2.2016).

Due to various approval situations and limited availability of imaging modalities at some facilities and centers in Asian countries, it is difficult to establish the unified clinical practice guidelines for bladder cancer in Asia or introduce the western guidelines directly into Asian countries. However, a consensus has been reached based on data and experience from the Asian region. Both MVAC and GC are available in Asian countries including India, Japan, South Korea, Singapore, Indonesia, Malaysia, Philippines, Thailand, etc. In some Asian countries, GC is the 1st-line chemotherapy. Growth factor support in the treatment of MVAC depends on the patient's condition (NCCN Guidelines - Asia Consensus Statements: Version 1, 2016: Bladder Cancer Version 1.2016).

At present the first-line standard of care available in China for patients with metastatic or unresectable bladder cancer includes: GC, TCG (pactitaxel + cisplatin + gemcitabine) and DD-MVAC. For patients who are not able to tolerate the standard 1st-line treatment, alternative therapies including carboplatin, oxaliplatin, gemcitabine monotherapy, docetaxel monotherapy or paclitaxel monotherapy will be applied. Objective response rate (ORR) in first line setting is approximately 50-60%, median progression-free survival (PFS) ranges from 7-9 months and median overall survival (OS) from 12-16 months (Sheng 2016).

Currently, the most frequently used the second-line treatments include docetaxel, paclitaxel or pemetrexed, however there is no consistent standard of care following the second line. The efficacy data of the second-line treatment reported in China is very limited, but according to the data reported in the United States and Europe, the ORR is approximately 10% (Oing 2016) and median PFS and OS are short, 2-3 months and 5-7 months respectively. Given the safety profile of these agents, additional treatments should be tested, as advanced bladder cancer is a serious unmet medical need for which there are few effective therapies. (Loehrer 1992).

There are few drugs approved for the treatment of patients with bladder cancer. Ever since cisplatin was approved as a first-line treatment by the US FDA in 1978, no other novel drug has been approved in the US; gemcitabine was approved by European Medicines Agency in 2008 for the usage in combination with cisplatin and vinflunine in 2009 in the second line. On May 18th, 2016, atezolizumab was granted accelerated approval by US FDA for treating second-line UBC, and represents a breakthrough in immunotherapy targeting advanced bladder cancer.

1.3. Targeted Therapy for Urothelial Bladder Cancer

Although there is an increasing understanding of the molecular biology and signaling pathways underlying bladder cancer development and progression (particularly the fibroblast growth factor receptor-, vascular endothelial growth factor-, and epidermal growth factor receptor-pathways), no targeted agents currently have a role in the treatment of UBC.

1.4. Immunotherapy in Urothelial Bladder Cancer

Immune check point-inhibitory receptor, programmed cell death-1 (PD-1) is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes. It

is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes (TIL), while the expression of PD-1 ligand, program death ligand-1 (PD-L1), is significantly increased in tumor cells (TCs) and tumor-associated immune cells (ICs) in the presence of stimulating cytokines such as interferon (IFN)-α and IFN-γ in the tumor microenvironment. Furthermore, the increased PD-1 expression in TIL and/or PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human tumors. This evidence provided the basis for cancer immunotherapeutic intervention via the approach of antagonizing PD-1.

Atezolizumab was granted accelerated approval by US FDA based on a Phase 2 single-arm study (IMvigor210, Table 1). After a median follow-up of 14 months, efficacy data this revealed an ORR of 15% with median duration of response (DOR) not reached (2.1+~13.8+ months) in all 310 patients. Among 46 patients with confirmed responses, the DORs were over 6 months in 37 patients; and 6 patients had DORs longer than 12 months. Given the low ORR, short DOR, high toxicity and insignificant improvement in OS of other second-line therapies treating advanced bladder cancer, atezolizumab has significantly increased ORR, as well as extended DOR, supporting the accelerated approval designation. The subgroup analysis based on the expression of PD-L1 in ICs indicated that the ORR of the 100 patients in the IC2/3 (PD-L1 ≥ 5%) cohort was 26% (95% CI 18-36%) and ORR of the 207 patients in the IC1/2/3 (PD-L1≥1%) cohort was 18% (95% CI 13-24%), which strongly supported the correlation between the expression of PD-L1 and ORR.

Data from a Phase 1 trial of an anti-PD-L1 antibody durvalumab (Study 1108, Table 1) demonstrated an ORR of 31% (95% CI 18-47). The median DOR was not reached (1.0+~12.3+ months) in the 42 patients enrolled and treated. The subgroup analysis based on the expression of PD-L1 in both TCs and ICs indicated that the ORR in the PD-L1 positive (TCs/ICs ≥ 25%) cohort (n=28) was 46% (95% CI: 28-66%) and 0% (95% CI: 0-23%) in the PD-L1 negative (TCs & ICs < 25%) cohort (n=14).

In addition, nivolumab was evaluated in patients with advanced UBC who had at least received once platinum-containing chemotherapy (CheckMate 032, Table 1). Among the 78 patients enrolled, the ORR was 24.4% (95% CI: 15.3-35.4). The ORR in the PD-L1-negative subset (PD-L1 <1%; n=42) was 26.2% (95% CI: 13.9-42.0%) and 24.0% (95% CI: 9.4-45.1%) in the subset of 25 patients whose tumors had PD-L1 expression ≥ 1%. Median DOR was 9.4 months (5.7-12.5 months). Another Phase 2 single-arm study of nivolumab (CheckMate 275, Table 1) in the second-line treatment setting reported an ORR of 19.6% (95% CI: 15.0-24.9%) (n=265). The ORR in the PD-L1 < 1% cohort (n=143) was 16.1% (95% CI: 10.5-23.1%) and 23.8% (95% CI: 16.5-32.3%) in the PD-L1 ≥ 1% cohort (n=122). The ORR in the PD-L1 < 5% cohort (n=184) was 15.8% (95% CI: 10.8-21.8%) and 28.4% (95% CI: 18.9-39.5%) in the PD-L1 ≥ 5% cohort (n=81). DOR was not reached with a median follow-up of over 7 months and 76.9% of the responders had not progressed.

A Phase 1b study of another anti-PD-1 antibody pembrolizumab (Keynote-012, Table 1) involving multiple indications was reported at ASCO in 2015, showing that among 29 evaluable

patients with advanced UBC, the ORR reached 27.6% (95% CI: 12.7-47.2%) with DOR ranging from 2.0 to 16.0+ months and median OS reached 12.7 months.

In summary, there has been reported efficacy data suggesting that higher expression of PD-L1 is likely associated with higher ORR among patients with UBC. In addition, encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that anti-PD-1/PD-L1 antibodies can result in a significant clinical benefit in patients with UBC.

Table 1 Summary of Reported Efficacy Data for PD-1/PD-L1 Antibodies

Drug	Trial ID	Phase	PD-L1 Ab	Sample Size	ORR, % (95% CI)	Median DOR, months (range)	Median PFS, months (95% CI)	Median OS, month (95% CI)	Data Source
Atezolizumab	IMvigor210	2	Ventana (SP142)	**310 (all patients)**	**14.8 (11.1, 19.3)**	**NR (2.1+, 13.8+)**	**2.1 (2.1, 2.1)**	**7.9 (6.6, 9.3)**	Rosenberg 2016
				210 (PD-L1<5% in IC)	9.5 (5.9, 14.3)	12.7 (2.1+, 12.7)			
				100 (PD-L1≥5% in IC)	26.0 (17.7, 35.7)	NR (4.2, 13.8+)	2.1 (2.1, 4.1)	11.4 (9.0, NE)	
Durvalumab	Study 1108	1	Ventana (SP263)	**42 (all patients)**	**31 (17.6, 47.1)**	**NR (1.0+, 12.3+)**			Massard 2016
				14 (PD-L1<25% in TC and IC)	0.0 (0.0, 23.2)				
				28 (PD-L1≥25% in TC or IC)	46.4 (27.5, 66.1)				
Nivolumab	CheckMate 032	1/2	Dako (28-8)	**78 (all patients)**	**24.4 (15.3, 35.4)**	**9.4 (5.7, 12.5)**	**2.8 (1.5, 5.9)**	**9.7 (7.3, 16.2)**	Sharma 2016
				42 (PD-L1<1%)	26.2 (13.9, 42.0)		2.8 (1.4, 6.5)	9.9 (7.0, NE)	
				25 (PD-L1≥1%)	24.0 (9.4, 45.1)		5.5 (1.4, 11.2)	16.2 (7.6, NE)	
	CheckMate 275	2	Dako (28-8)	**265 (all patients)**	**19.6 (15.0, 24.9)**	**NR**	**2.0 (1.9, 2.6)**	**8.7 (6.1, NE)**	Galsky 2016
				143 (PD-L1<1%)	16.1 (10.5, 23.1)				
				122 (PD-L1≥1%)	23.8 (16.5, 32.3)				
				184 (PD-L1<5%)	15.8 (10.8, 21.8)				
				81 (PD-L1≥5%)	28.4 (18.9, 39.5)				
Pembrolizumab	KEYNOTE-012	1b	Dako (22C3)	**29 (all patients)**	**27.6 (12.7, 47.2)**	**NR (2.0, 16.0+)**	**2.0 (1.7, 4.0)**	**12.7 (5.0, NR)**	Plimack, 2015
				11 (PD-L1<1% in TC)	9 (0, 41)				
				18 (PD-L1≥1% in TC)	33 (13, 59)				
				4 (PD-L1<1% in TC and IC)	0 (0, 60)				
				24 (PD-L1≥1% in TC and IC)	29 (13, 51)				

Abbreviations: Ab, antibody; CI, confidence interval; DOR, duration of response; IC, immune cell; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, program death ligand-1; PFS, progression-free survival; TC, tumor cell.

1.5. Background Information on Tislelizumab

1.5.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1. It is being developed for the treatment of human malignancies.

Tislelizumab binds to the extracellular domain of human PD-1 with high specificity and affinity (dissociation constant [K_D] = 0.15 nM) as demonstrated by receptor binding assays based on Surface Plasmon Resonance. It competitively blocks the binding of both PD-L1 and program death ligand-2 (PD-L2), inhibiting PD-1 mediated negative signaling in T-cells. In in vitro cell-based assays, the humanized antibody consistently and dose-dependently enhanced the functional activity of human T-cells and pre-activated, primary PBMCs (peripheral blood mononuclear cells). In addition, tislelizumab demonstrated anti-tumor activity in several human cancer allogeneic xenograft models, including A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 non-small cell lung cancer models, where the PBMCs were co-injected with the human cancer cells (A431) or the tumor fragments (BCCO-028 and BCLU-054) into the immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to Fc (fragment crystallizable region) gamma receptor (FcγR) IIIA and complement 1q (C1q) by in vitro assays, suggesting a low or no antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity effect in humans (Labrijn et al 2009).

Please refer to the tislelizumab investigator's brochure (IB) (BeiGene Investigator's Brochure, BGB-A317) for additional details regarding nonclinical studies of tislelizumab.

1.5.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single dose toxicology studies in mice and monkeys and in a 13-week repeat dose toxicology study in monkeys. The tissue cross reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood and PBMC. The pivotal studies were conducted following good laboratory practices regulations. The single dosing levels were spanning from the intended human doses to 10 folds higher than the maximum of the intended human doses, and the repeat dosing levels spanning to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

No apparent toxicity or target organs were noted or identified in mice or monkeys. No specific tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assay or PBMC assay. Toxicokinetic profile was well characterized with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent effect on the systemic exposure. The No Observed Adverse Effect Level of tislelizumab in 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study BGB-A317-204.

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

1.5.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim pharmacokinetics (PK) analysis (data cutoff date 28 August 2017) was conducted using noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, and 2.0 mg/kg, 5.0 mg/kg, and 200 mg once every 3 weeks (Phase 1a Parts 1, 2, and 3, and Phase 1b in BGB-A317_Study_001), and patients who received doses of 200 mg once every 3 weeks in Phase 1 of Study BGB-A317-102 (n=19). The maximum observed plasma concentration and the area under the plasma or serum concentration-time curve increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration at steady state. Preliminary PK data from 27 patients who were administered 1 dose of 200 mg once every 3 weeks (Phase 1a, Part 3 and Study BGB-A317-102) showed tislelizumab concentrations between the range of concentrations observed for patients who were administered 2 mg/kg and 5 mg/kg doses.

Preliminary population PK analysis using a 2-compartment model with first-order elimination shows a systemic plasma clearance of tislelizumab of 0.173 L/day, volume of distribution in the central and peripheral compartments of 2.89 L and 1.76 L, respectively, and half-life of approximately 19 days. Race, gender, and body weight were not significant covariates on the clearance of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.5.4. Prior Clinical Experience of Tislelizumab

As of 28 February 2018, there are 13 ongoing studies with tislelizumab, including monotherapy and combination studies in solid tumors and hematological malignancies. Of the ongoing monotherapy studies in solid tumors, available data from BGB-A317_Study_001 and BGB-A317-102 are summarized below (with a data cutoff date of 28 August 2017).

Please refer to the tislelizumab IB (BeiGene Investigator's Brochure, BGB-A317) for more detailed information on efficacy and safety of tislelizumab.

1.5.4.1. BGB-A317_Study_001 (Data Cutoff 28 August 2017)

Study BGB-A317_Study_001 is a 2-stage study consisting of a Phase 1a dose-escalation and dose-finding component with 3 parts to establish the maximum tolerated dose, if any, a recommended Phase 2 dose for the Phase 1b, and a flat dose (fixed dose) followed by a Phase 1b component to investigate efficacy in select tumor types in indication expansion arms and to further evaluate safety and tolerability of tislelizumab.

As of 28 August 2017, in Phase 1a, 116 patients had received tislelizumab at dose regimens including 0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg once every 2 weeks; 2 mg/kg or 5 mg/kg once every 3 weeks; and 200 mg once every 3 weeks. In Phase 1b, 323 patients had received tislelizumab in Phase 1b across 9 indication-expansion cohorts.

Overall, for the 439 patients in the study, the median age was 60.0 years, 53.8% of the population was male, and 65.6% of patients were white. The median number of prior anticancer therapy regimens was 2 (range: 0 to 12). The median treatment exposure duration was

2.50 months (range: 0 to 23.0), and the median study follow-up duration was 5.56 months (range: 0.0 to 26.9). As of 28 August 2017, there were 210 patients (47.8%) remaining on study in Study BGB-A317_Study_001.

Preliminary Safety

Of the 439 total patients in the Safety analysis set for BGB-A317_Study_001, 240 (54.7%) experienced at least 1 treatment-emergent adverse event (TEAE) assessed as related to tislelizumab by the investigator and 34 (7.7%) experienced at least 1 ≥ Grade 3 related TEAE. The most commonly occurring related TEAEs for patients treated with the tislelizumab monotherapy in BGB-A317_Study_001 were fatigue (12.8%), rash (7.7%), nausea (6.8%), diarrhoea (6.6%), and hypothyroidism (4.8%). The ≥ Grade 3 related TEAEs occurring in ≥ 2 patients were pneumonitis (6 patients, 1.4%); colitis and alanine aminotransferase (ALT) increased (4 patients each, 0.9%); fatigue, type 1 diabetes mellitus, and aspartate aminotransferase (AST) increased (3 patients each, 0.7%); and diarrhoea, gamma-glutamyltransferase increased, and diabetic ketoacidosis (2 patients each, 0.5%). All other events occurred in single patients. Lastly, 18 patients (4.1%) experienced an infusion-related reaction; all were mild/moderate in severity.

Preliminary Efficacy

For patients in Phase 1a (n=116, evaluable), there were 20 patients with a confirmed response and 42 patients with a best overall response (BOR) of stable disease (SD).

For patients in Phase 1b (n=286 evaluable), a total of 26 patients had a confirmed response. Additionally, there were 101 patients with a BOR of SD.

1.5.4.2. Study BGB-A317-102 (Data Cutoff 28 August 2017)

This Phase 1/2 study was a dose verification of tislelizumab and an indication-expansion study of tislelizumab conducted in Chinese patients with advanced solid tumors.

Overall, for the 123 patients in Study BGB-A317-102, the median age was 54.0 years, 66.7% of the population was male, and 100% of patients were Asian (Chinese). The median number of prior anti-cancer therapy regimens was 2 (range: 0 to 9). The median treatment exposure duration was 1.78 months (range: 0 to 8.0), and the median study follow-up duration was also 1.78 months (range: 0.0 to 8.0). As of 28 August 2017, there were 113 patients (91.9%) remaining on study in Study BGB-A317-102.

Preliminary Safety

Of the 123 total patients in the Safety analysis set for Study BGB-A317-102, 69 (56.1%) experienced at least 1 TEAE assessed as related to tislelizumab by the investigator and 10 (8.1%) were ≥ Grade 3 in severity. The most commonly occurring related TEAEs were AST increased (20 patients, 16.3%), ALT increased (17 patients, 13.8%), and blood bilirubin increased and anaemia (13 patients each, 10.6%). The ≥ Grade 3 related TEAEs occurring in ≥ 2 patients were AST increased (3 patients, 2.4%) and ALT increased (2 patients, 1.6%). All other events occurred in single patients, including a case of retinal detachment (Grade 4).

Preliminary efficacy data are not yet available.

1.5.4.3. Immune-Related Reactions

In patients treated with tislelizumab monotherapy, the following immune-related adverse events (irAEs) were observed:

- Acute hepatitis and abnormal liver function have been reported, including 1 patient with fatal hepatitis. Additionally, 3.2% of patients experienced treatment-related abnormal liver function tests, and 1.4% of patients experienced immune-related hepatitis or hyperbilirubinaemia.
- Pneumonitis has been reported in 2.1% of patients, including 1 patient with fatal pneumonitis.
- Colitis has been reported in approximately 2% of patients treated. Diarrhoea has been reported in 6.6% of patients.
- Endocrinopathies have been reported including diabetes mellitus (hyperglycemia and ketoacidosis). In addition, thyroiditis, including thyrotoxicosis and hypothyroidism has been reported. Furthermore, hypophysitis has been reported in < 1% of patients treated.
- Other immune-related events (< 1% of patients with tislelizumab monotherapy except where noted): skin reactions (20.5%, including rash and pruritus); arthralgia (2.5%); haemolytic anaemia, nephritis, proteinuria (1.8%); encephalitis, neuropathy, arthritis, pancreatitis, stomatitis, uveitis, and dry eye (1.4%).

Beyond patients treated with tislelizumab monotherapy, a case of fatal myocarditis and polymyositis was reported in 1 patient who received a single dose of tislelizumab, in combination with paclitaxel and cisplatin. The patient's initial symptoms were dyspnea and tea-colored urine 2 weeks after starting treatment. Elevated urine and serum cardiac and skeletal muscle enzymes were reported. The patient died of multi-organ failure 6 days later.

1.6. Study Rationale and Benefit-Risk Assessment

Comparing with currently available therapies, anti-PD-1/PD-L1 antibodies approved or currently under clinical trials have already demonstrated significant clinical benefit in the population of patients with metastatic or unresectable UBC. Reported data of anti-PD-1/PD-L1 antibodies, such as atezolizumab, nivolumab and pembrolizumab, has demonstrated favorable efficacy (See Section 1.4). In addition, data has been reported that PD-L1 could be employed as a biomarker to predict better efficacy among 2nd-line patients with UBC (Table 1). Also, PD-L1 expression has been detected in UBC with high mutation rate, which is another factor considered to be related to better response to the immune checkpoint inhibitors.

According to the latest data collected from BGB-A317_Study_001, the early anti-tumor activity of tislelizumab, including in UBC, has been observed. Preliminary data from the ongoing Phase 1 and Phase 2 studies show the safety profile of tislelizumab is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3/4 irAEs have been observed, and they have been generally reversible and manageable with study drug

interruption and/or steroid treatment. For further information on the safety profile of tislelizumab, please refer to the IB (BeiGene Investigator's Brochure, BGB-A317).

Given the lack of standard of care for the 2nd-line patients with UBC in Asia, as well as the low ORR and short PFS/OS provided by therapies currently available, the benefit/risk assessment of this study, ie, tislelizumab treating patients with previously treated, program death ligand-1 positive (PD-L1+) locally advanced or metastatic UBC, is considered as acceptable to support further clinical study.

2. OBJECTIVES

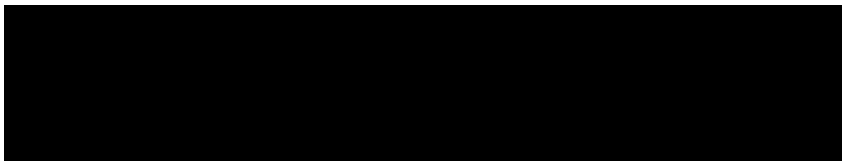
2.1. Primary Objective

- To determine the efficacy of tislelizumab in patients with previously treated, PD-L1+, locally advanced or metastatic UBC, as measured by the ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessed by independent review committee (IRC)

2.2. Secondary Objectives

- To evaluate the efficacy of tislelizumab as measured by DOR, PFS, and disease control rate (DCR) according to RECIST version 1.1 assessed by IRC
- To evaluate the efficacy of tislelizumab as measured by OS
- To evaluate the efficacy of tislelizumab as measured by ORR, DOR, PFS and DCR according to RECIST version 1.1 and immune-related RECIST (irRECIST) assessed by investigators
- To evaluate the safety and tolerability of tislelizumab as determined by the frequency and severity of adverse events (AEs) according to National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) version 4.03, and the rate of discontinuation of treatment due to AEs

2.3. Exploratory Objectives



3. STUDY DESIGN

3.1. Description of Study

3.1.1. Initial Treatment Stage

This is a single-arm, multicenter Phase 2 study to evaluate the efficacy and safety of the anti-PD-1 monoclonal antibody tislelizumab in participants with PD-L1+ locally advanced or metastatic UBC who have progressed during or following a platinum-containing regimen. The study is composed of an initial screening phase (up to 28 days), a treatment phase (until disease progression, intolerable toxicity, or treatment withdrawal for other reasons), safety follow up phase, and survival follow-up phase.

Approximately 110 patients will be allocated to receive tislelizumab 200 mg IV every 3 weeks. Radiological assessment of tumor-response status should be performed every 9 weeks (±1 week). Tumor response will be assessed by IRC based on the RECIST version 1.1, and by investigators based on RECIST version 1.1 and irRECIST. Pseudo-progression may occur due to IC infiltration and other mechanisms as manifested by apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, for progressive disease (PD) suspected by the investigator as pseudo-progression, treatment may continue until confirmation of PD with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point, but not to exceed 12 weeks from the initial documentation of PD. The patient must be re-consented and the following criteria must be met in order to continue the treatment after initial PD: a. Absence of clinical symptoms and signs of disease progression (including clinically significant worsening laboratory values). b. Stable ECOG performance status. c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention.

Patients will be evaluated for AEs (all grades, according to NCI-CTCAE version 4.03), serious adverse events (SAEs), and any AE that leads to treatment discontinuation will be followed up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline or ≤ Grade 1, the investigator assesses the event 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 AE. Immune-related adverse events will be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days, and 90 days (± 14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected irAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

If a patient discontinues study treatment due to the reason other than disease progression or death, then tumor assessments should continue to be performed following the scheduled

assessment plan until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawn consent.

3.1.2. Independent Review Committee

An IRC will be established to perform an independent review of all radiological scans for the efficacy analysis and to determine the response and disease progression on the basis of the RECIST version 1.1 in addition to the local investigator's review of radiographs. Only the results from the investigator's review of radiographs will be used to determine whether patients should be enrolled or should remain in the study. The IRC's assessment will only be used in the efficacy analysis. All decisions made during the performance of the study will be on the basis of the local investigator's review and assessment of radiographs. Sites will submit radiological files to the centrally located IRC's data review facility during the study on an ongoing basis or at the sponsor's request for efficacy analysis. Detail rules and guidelines on IRC tumor assessments are outlined separately in an IRC Charter.

Because the China National Medical Products Administration (NMPA) approved the urothelial carcinoma indication for tislelizumab on 09 April 2020, and the Center for Drug Evaluation (CDE) of the NMPA had agreed that "IRC tumor assessment will not be required after 16 September 2019," tumor responses are not assessed by the IRC after 16 September 2019.

3.2. End of Study

The end of study is defined as the date of the last follow-up visit. Primary efficacy analysis of ORR will be conducted no later than 6 months after the first dose of the last patient. The study will continue until the last data point from the last patient (OS) is received. The survival information of each patient will be collected until death, loss to follow up, withdrawal of consent, or study termination by the sponsor. The sponsor may terminate the study at any time.

3.3. Rationale for Study Design

3.3.1. Rationale for PD-L1 Selection in Urothelial Bladder Cancer

Despite recent improvements in treatment, the prognosis for patients with advanced UBC remains dismal, with median OS of approximately 15 months (Garcia 2006). Patients who receive 2nd-line treatment for their disease have an even more limited prognosis, with median survival duration of approximately 7-9 months (Sonpavde 2010). Approved therapies are associated with significant toxicities (eg, neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life. Therefore, there is a continuing need for more efficacious, better-tolerated treatments for patients with advanced UBC.

Inhibition of PD-L1/PD-1 signaling has been shown to produce durable responses in some patients. Expression of PD-L1 by TCs in several tumor types has been shown to correlate with response to therapy (Topalian 2012). Published results suggest in bladder cancer that expression of PD-L1 in tumors correlates with response to anti-PD-1 or anti-PD-L1 therapy (Balar 2016; Galsky 2016; Loriot 2016; Massard 2016; Rosenberg 2016).

On the basis of these observations, this study will select PD-L1 high patients to achieve greater clinical benefit. The PD-L1 expression status will be measured by immunohistochemistry assay

in a central laboratory and using Ventena PD-L1 (SP263) antibody. According to published data from duvalumab using the same antibody (Massard 2016), PD-L1 is defined as high if ICs involve >1% of the tumor area, either ≥25% of TCs or ≥25% of ICs express PD-L1; if ICs involve ≤1% of the tumor area, TCs ≥25% or ICs=100%. And PD-L1 is defined as low/negative if did not meet criterion for PD-L1 high. Meanwhile, the relationship between PD-L1 status (as determined by immunohistochemistry) and efficacy in patients with UBC is still being investigated in other ongoing studies of tislelizumab. Criteria of PD-L1 positivity might be adjusted based on further findings.

3.3.2. Rationale for Tislelizumab Dosage

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

Simulations do not suggest any clinically meaningful differences in exposure following fixed dose or dose adjusted for weight (Bai 2012). On the basis of this analysis, a fixed dose of 200 mg is selected (equivalent to a body weight−based dose of 3.3 mg/kg, calculated with 60 kg).

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

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

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

In conclusion, tislelizumab 200 mg once every 3 weeks is the recommended dose for pivotal studies.

3.3.3. Rationale for Pharmacokinetic Evaluation Schedule

The proposed sampling scheme for tislelizumab concentration assessments will contribute to the characterization of tislelizumab PK. The tislelizumab concentration results may be compared with available data from other tislelizumab clinical studies and correlated with safety events in this study as appropriate.

3.3.4. Rationale for the Use of Modified Response Criteria (Immune-Based)

Cancer immunotherapies may result in early apparent radiographic progression (pseudo-progression/tumor immune infiltration), including the appearance of new lesions, followed by delayed response (Wolchok 2009). Additionally, responding tumors may appear to increase in size because of the influx of ICs (Hoos 2010). Unconventional response patterns have been described in patients treated with anti-cytotoxic T lymphocyte-associated antigen 4 (Wolchok 2009). Therefore, irRECIST will be used in this study to accommodate the possible appearance of new lesions and to allow the apparent increase in tumor burden to be confirmed at a subsequent assessment prior to designation of PD. This study is designed to characterize these different patterns of response and will provide supportive clinical evidence.

3.4. Study Endpoints

3.4.1. Primary Endpoints

- ORR – defined as the proportion of patients who had confirmed complete response (CR) or PR assessed by IRC using RECIST version 1.1

3.4.2. Secondary Endpoints

Efficacy:

- DOR – defined as the time from the first determination of a confirmed objective response by IRC according to RECIST version 1.1 until the first documentation of progression or death, whichever comes first
- PFS – defined as the time from date of first dose of study drug to date of first documentation of disease progression assessed by IRC using RECIST version 1.1 or death, whichever occurs first
- DCR – defined as the proportion of patients who achieve CR, PR, and SD assessed by IRC using RECIST version 1.1
- OS – defined as the time from the date of first dose of study drug until date of death from any cause
- ORR, DOR, PFS and DCR assessed by investigator per RECIST version 1.1 and irRECIST respectively

Safety:

To evaluate the safety and tolerability of tislelizumab, as defined by:

- The incidence and severity of AEs according to NCI-CTCAE version 4.03
- Changes in vital signs, physical findings, and clinical laboratory results

3.4.3. Exploratory Endpoints

- [redacted]

- [redacted]
- [redacted]

4. MATERIALS AND METHODS

4.1. Study Population

4.1.1. Inclusion Criteria

1. Patients with histologically or cytologically documented locally advanced (T4b, any N; or any T, N2-3) or metastatic (M1, Stage IV) TCC of the urothelium (including renal pelvis, ureters, urinary bladder, urethra)
2. Disease progression during or following treatment with at least one platinum-containing regimen for inoperable locally advanced or metastatic urothelial carcinoma or disease recurrence
   a. Patients who received prior neoadjuvant or adjuvant chemotherapy and progressed within 12 months of treatment with platinum-containing regimen will be considered as second-line patients
   b. Patients intolerant to platinum-containing regimen due to Grade 4 hematologic toxicity or Grade 3 or 4 non-hematologic toxicity may also be eligible

   Note: No more than 2 prior lines of systemic therapy for metastatic UBC
3. Patients must submit archival tumor tissue (formalin-fixed paraffin-embedded block containing tumor [preferred] or at least 5 unstained slides) with an associated pathology report, or agree to a tumor biopsy for determination of PD-L1 expression and other biomarker analyses (fresh tumor biopsies are strongly recommended at baseline in patients with readily accessible tumor lesions and who consent to the biopsies). PD-L1 expression will be assessed centrally, and patients who are tested as PD-L1 high are eligible

   PD-L1 expression is defined as high:

   - If ICs involve >1% of the tumor area, either ≥ 25% of TCs or ≥ 25% of ICs express PD-L1
   - If ICs involve ≤ 1% of the tumor area, TCs ≥25% or ICs=100%

   And PD-L1 expression is defined as low/negative if it did not meet the criterion for PD-L1 high.

   Note: Tumor tissue should be of good quality based on total and viable tumor content.
4. Patients must have at least one measurable lesion as defined per RECIST version 1.1 assessed by the investigator (Imaging report must be submitted to the sponsor medical monitor to permit review of measurable disease at baseline)
5. Male or female, aged ≥ 18 years on day of signing informed consent
6. Patients have voluntarily agreed to participate by giving written informed consent
7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
8. Life expectancy ≥ 12 weeks

9. Patient must have adequate organ function as indicated by the following screening laboratory values obtained within 7 days prior to the first study treatment
    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    b. Platelets $\geq 100 \times 10^9$/L
    c. Hemoglobin ≥9 g/dL or ≥5.6 mmol/L (Note: Criteria must be met without a transfusion within 14 days of obtaining the sample)
    d. Calculated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula, see Appendix 5)
    e. Serum total bilirubin ≤ 1.5 X upper limit of normal (ULN) (total bilirubin must be <4 X ULN for patients with Gilbert's syndrome)
    f. Aspartate aminotransferase (AST) and ALT ≤ 2.5 X ULN OR ≤ 5 X ULN for patients with liver metastases
10. Female patients are eligible to enter and participate in the study if they are of:
    a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant), including any female who
        i. Has had a hysterectomy
        ii. Has had a bilateral oophorectomy (ovariectomy)
        iii. Has had a bilateral tubal ligation
        iv. Is post-menopausal (total cessation of menses for ≥1 year)
    b. Childbearing potential, has a negative serum pregnancy test at screening (within 7 days before the first investigational product administration), not be breast feeding, and agree to remain abstinent (refrain from heterosexual intercourse) or uses adequate contraceptive methods that result in a failure rate of <1% per year before study entry and throughout the study until 120 days after the last investigational product administration

        Note: Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
11. Male patients are eligible to participate in the study if they are vasectomized or agree to use contraception during the study treatment period and for at least 120 days after the last dose of study drug

4.1.2. Exclusion Criteria

1. History of severe hypersensitivity reactions to other humanized monoclonal antibodies
2. Prior active malignancy within 2 years prior to Cycle 1 Day 1, exceptions include the tumor under investigation in this study, localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse, and locally recurring cancers that have undergone curative intent treatment, such as resected basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast

3. Prior therapies targeting PD-1 or PD-L1
4. Active brain or leptomeningeal metastases as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening and prior radiographic assessments. Patients with brain metastases are permitted if they are asymptomatic, eg, diagnosed incidentally at screening by brain MRI, or patients with previously treated brain metastases that is asymptomatic, radiographically stable and not requiring steroid medications for at least 4 weeks prior to Cycle 1 Day 1
5. Patients with active autoimmune diseases or history of autoimmune diseases that may relapse should be excluded (see Appendix 4 for a more comprehensive list of autoimmune diseases). Patients with the following diseases are allowed to be enrolled for further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), controlled celiac disease, or diseases not expected to recur in the absence of external triggering factors
6. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration

   Note: Adrenal replacement doses ≤ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease; patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted
7. Has history of interstitial lung disease or non-infectious pneumonitis except for those induced by radiation therapies
8. With severe chronic or active infections (including tuberculosis infection, etc) requiring systemic antibacterial, antifungal or antiviral therapy within 14 days prior to first dose of study drug.
9. With uncontrollable pleural effusion, pericardial effusion or ascites requiring pleurocentesis or abdominal tapping less than 4 weeks
10. Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within the previous 3 months, unstable arrhythmias, or unstable angina

    Note: Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate
11. Known history of Human Immunodeficiency Virus (HIV)
12. Patients with untreated chronic hepatitis B or chronic HBV carrier with HBV DNA ≥500 IU/mL (or 2.5×10^3 cps/mL), or active hepatitis C should be excluded. Patient with inactive HBsAg carrier, active HBV infection with sustained anti-HBV suppression

(HBV DNA <500 IU/mL or 2.5×10^3 cps/mL) and patients whose hepatitis C has been cured (HCV RNA is lower than detection limit) can be enrolled

13. Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or AEs
14. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies (including Chinese herbal medicine and Chinese patent medicines) used to control cancer within 2 weeks of Cycle 1 Day 1. AEs associated with these therapies must be Grade 0-1, baseline or stabilized (except for alopecia)
15. Prior allogeneic stem cell or solid organ transplant
16. Administration of a live or attenuated vaccine within 4 weeks prior to study drug administration
17. Major surgical procedure other than for diagnosis within 28 days prior to study drug administration

4.2. Method of Treatment Assignment and Blinding

This is a single-arm Phase 2 study.

Each patient enrolled in this study will receive a unique patient number after signing the informed consent. Each patient receiving tislelizumab will be identified by this unique number. Once this unique patient number has been assigned to a patient, it cannot be reassigned to any other patient.

4.3. Study Treatment

4.3.1. Formulation, Packaging, and Handling

Tislelizumab is a monoclonal antibody drug which is formulated for IV injection in a sterile, single-use vial containing a total of 100 mg antibody in 10 mL of isotonic solution.

Tislelizumab was aseptically filled in 20R glass vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial contains 10 mL of the drug solution. The vials were packaged in carton.

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

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

The investigational product must be kept at the temperature condition as specified on the label.

Refer to the pharmacy manual for details regarding IV administration, accountability, and disposal. Please also refer to the IB (BeiGene Investigator's Brochure, BGB-A317) for other details regarding tislelizumab.

4.3.2. Dosage, Administration, and Compliance

The dose level of tislelizumab in this study is 200 mg administered every 3 weeks (Q3W).

Tislelizumab will be administered by IV infusion, using a volumetric pump through an IV line containing a sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the pharmacy manual. The initial infusion will be delivered over 60 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 30 min, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 4.4). Use of a volumetric pump was recommended to control the infusion speed and to avoid potential infusion reactions associated with too rapid administration. The pump may not be needed if the infusion speed is controlled through alternative means and consistent with approved institutional procedures. However, tislelizumab drug solution must still be infused at the speed ≥ 60 minutes for the 1st infusion time or ≥ 30 minutes in the 2nd time of infusion and thereafter. As well, the IV administration line must be equipped with a sterile, non-pyrogenic, low-protein binding 0.2 or 0.22 micron in-line or add-on filter as described in the coincident protocol.

As a routine precaution, after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

Guidelines for dosage modification, treatment interruption or discontinuation and for the management of irAEs and infusion-related reactions are provided in Section 5.3.1, Section 5.3.2, and Appendix 6.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the AE eCRF.

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

4.4. Concomitant Therapy

4.4.1. Permitted Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (eg, such as anti-emetics, anti-diarrhea) and safety of the patient are allowed. All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

All concomitant medications received within 30 days before the first dose of study medication and 30 days after the last infusion of study medication should be recorded. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug regardless of whether or not the patient starts a new anticancer therapy.

The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medication.

Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered gradually (see Appendix 6) be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next study drug administration. The use of steroids as prophylactic treatment for patients with contrast allergies to diagnostic imaging contrast dyes will be permitted.

Patients may continue to receive hormone replacement if initiated prior to enrollment. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to enrollment.

Whole brain radiation therapy and/or stereotactic radiosurgery are permitted for patients with progressive central nervous system (CNS) metastasis, but only for patients who have clinical benefit outside the brain. Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline and only if all of the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion
- The case is discussed with the sponsor medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met

4.4.2. Prohibited Concomitant Medications/Procedures

The following medications and procedures are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and Chinese patent medicines] for treatment of cancer).
- Live or attenuated vaccines within 28 days prior to the first dose of study therapy and 60 days of last dose. Examples of live or attenuated vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.
- Major surgery (excluding prior diagnostic biopsy or placement of a venous access device).
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or known to potentially interfere with major organ function (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study.

4.4.3. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).

- Systemic corticosteroids > 10 mg daily (prednisone equivalent), except to treat a drug-related AE (per protocol) or for short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs during the study.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 4.4.1.

4.5. Study Assessments

Flowcharts of scheduled study assessments are provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

4.5.1. Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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.

Re-screening under limited conditions should be allowed after consultation with the sponsor, eg, when a patient narrowly misses a laboratory criterion and it's correctable and not due to rapidly deteriorating condition or PD. PD-L1 expression assessed by central laboratory during screening visit may be used rather than repeating tests. Multiple attempts should not be allowed for re-screening.

4.5.2. Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and all medications (eg, prescription drugs, OCT drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before the first dose.

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

Cancer history will include an assessment of prior platinum-containing treatment regimens, including start and stop dates, best response and reason for discontinuation.

4.5.3. Physical Examinations

During the screening visit, a complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE version 4.03 and recorded on the Medical History eCRF with appropriate disease/condition terms. Height and weight should be measured and recorded in the eCRF. Body mass index (in kg/m^2) should also be captured in the eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

4.5.4. Eastern Cooperative Oncology Group Performance Status

ECOG performance status (Table 2) will be assessed at the screening visit, prior to Day 1 of each treatment cycle, End of Treatment visit, and safety follow-up visit. If the screening laboratory assessment is performed ≤ 96 hours prior to the first administration of tislelizumab, they do not have to be repeated on Day 1 of Cycle 1 and will be used as baseline.

Table 2: ECOG Performance Status

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

4.5.5. Vital Signs

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

The patient's vital signs should be determined within 60 minutes before the infusion, and if clinically indicated during 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.

4.5.6. Tumor and Response Evaluations

Screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement.

A MRI or CT (with contrast if not contraindicated) scan of the brain must be done at screening to exclude CNS metastasis. An MRI scan of the brain is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal scan. Patients with CNS metastases if they are asymptomatic may be eligible for the study (see Section 4.1.2).

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when CR is identified in target disease or when progression in bone is suspected.

CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study if there is evidence of disease at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST version 1.1 may be used.

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to study entry may be used for the purposes of screening rather than repeating such tests.

For subsequent tumor assessments, the same radiographic procedure used to assess disease sites at screening should be used throughout the study (eg, the same contrast protocol for CT scans). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST version 1.1 and irRECIST (see Appendix 3 and Appendix 2, respectively). The same evaluator should perform assessments if possible to ensure internal consistency across visits. An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. It is recommended that the confirmatory tumor assessment is not left until the next scheduled CT scan, but be performed as soon as possible following the 28 days interval from the initial documentation of response. Tumor assessment will need to follow the original schedule after the confirmation scan.

At the investigator's discretion, radiographic scans should be repeated at any time if PD is suspected.

Patients who discontinue study treatment early during the initial treatment stage for reasons other than disease progression (eg, toxicity) should continue to undergo scheduled tumor assessments (every 9 weeks) until the patient begins a subsequent treatment, experiences disease progression, withdraws consent, dies, or until the study closes, whichever occurs first.

Patients who continue treatment beyond radiographic disease progression (see Section 4.6.2) will be monitored with a follow-up scan at least 4 weeks later or at the next scheduled tumor assessment (not exceed 12 weeks) before discontinuation of study treatment.

Scans will be submitted to an IRC for central review.

4.5.7. Laboratory, Biomarker, and Other Biological Samples

Local laboratory assessments will include the following:

- Hematology (complete blood count, including red blood cell [RBC] count, hemoglobin, hematocrit, white blood cell [WBC] count with differential [neutrophils, eosinophils, lymphocytes, monocytes, and basophils], and platelet count)
- Serum chemistries (glucose, blood urea nitrogen or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate [optional], calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase [LDH], amylase, total protein, albumin, creatine kinase [CK], and creatine kinase cardiac muscle isoenzyme [CK-MB]).
- Note: In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead; if only either troponin is assessed per local standards that same should be evaluated throughout.
- Coagulation panel (activated Partial Thromboplastin Time (aPTT) and prothrombin time (PT)/ international normalized ratio [INR])
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation)
- Urinalysis (specific gravity, pH, glucose, protein, ketones, blood, and microscopic examination including WBC/high power field (HPF), RBC/HPF, and any additional findings)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- HBV serology (HBsAg, antibodies against HBsAg, antibodies against hepatitis B core antigen [HBcAb])
- Patients who are HBsAg positive at screening must not be enrolled until further definite testing with HBV DNA titres can fulfill the criteria in Section 4.1.2.
- HCV serology (anti-HCV)
- Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

Central laboratories will coordinate the collection of archival tumor, fresh tumor, and leftover tumor tissue and blood samples for the assessment of tislelizumab PK, biomarkers and ADA assays. Instruction manuals and supply kits will be provided for all central laboratory assessments.

The following assessments will be performed at a central laboratory:

- ADA assays

  Serum samples will be assayed for the presence of ADAs to tislelizumab with use of validated immunoassays.

- PK assay

  Serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay.

4.5.8. Tumor Tissue Samples and Biomarkers Assessment

Archival tumor tissues (formalin-fixed paraffin-embedded block with tumor tissue [preferred] or around 15 unstained slides (at least 5 slides are required), or fresh biopsy need to be sent to central laboratory for PD-L1 status determination prospectively during screening (fresh tumor biopsies are strongly recommended at baseline or paired for biomarker analysis in patients with readily accessible tumor lesions and who consent to the biopsies). Tumor tissue samples will be assessed centrally for PD-L1 expression by immunohistochemistry with the Ventana SP263 assay optimized for use on the automated Bench Mark ULTRA platform (Ventana). PD-L1 expression for both TCs and ICs in the tumor microenvironment was determined by the percentage of cells expressing PD-L1 at any intensity above background staining. PD-L1 is defined as high:

- If ICs involve >1% of the tumor area, either ≥25% of TCs or ≥25% of ICs expressed PD-L1
- If ICs involve ≤1% of the tumor area, TCs ≥25% or ICs=100%

And PD-L1 is defined as low/negative if did not meet criterion for PD-L1 high, and patients are excluded if tested low/negative.

[redacted]

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Specimens from transurethral resection of bladder tumors without a muscle invasive component (ie, T2 or greater) are not acceptable; these patients will be required to submit an additional specimen obtained at the time of cystectomy/nephronureterectomy or metastatic spread (eg, sample from a metastatic lesion).

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.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

4.5.9. Cardiac and Pulmonary Function Tests

4.5.9.1. Electrocardiograms

A twelve-lead electrocardiogram (ECG) is required at screening, safety follow-up and as clinically indicated. ECGs should be obtained on the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any clinically significant morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.9.2. Pulmonary Function Tests

Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details).

4.5.10. Anti-Drug Antibody Testing

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

4.5.11. Assessments during Treatment

All visits must occur within ± 3 days from the scheduled date unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless a 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.

See the study flowchart provided in Appendix 1 for the schedule of treatment period assessments.

The following assessments may be performed ≤ 96 hours before Day 1 of each cycle: ECOG performance status, limited physical examination, local/central laboratory tests, AE evaluation, and concomitant medication evaluation.

If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 2 days, the patient can resume the original schedule.

Blood samples for PK will be obtained according to the schedule in Appendix 1.

The End of Treatment visit is conducted when the investigator determines that tislelizumab will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment visit, these tests need not be repeated. Tumor assessment is not required at the End of Treatment visit provided that fewer than 6 weeks have passed since the last assessment.

4.5.12. Safety Follow-up Visit

Patients who discontinue from treatment for disease progression will be asked to return to the clinic around 30 days after the last treatment for a safety follow-up visit, or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days, and 90 days (±14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. The End of Treatment visit at which a response assessment showed PD that results in patient discontinuation, may be used as the safety follow-up visit, if it occurred 30 days (± 7 days) after the last study treatment. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 4.5.6.

See the study flowcharts provided in Appendix 1 for assessments to be performed at the safety follow-up visit.

4.5.12.1. Adverse Events

All AEs (including SAEs [see Section 5.2.2] regardless of attribution, will be recorded until 30 days following their last dose of study treatment or until they receive another anti-cancer therapy, whichever comes first. Ongoing AEs thought to be related to study treatment 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. Immune-related adverse events will be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

4.5.13. Survival Follow-Up

Following discontinuation of the treatment, all patients will be followed for survival status beginning 3 months after safety follow-up visit or as directed by sponsor. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor.

4.6. Patient, Treatment, Study, and Site Discontinuation

4.6.1. Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study 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 continues in the study
- Investigator or sponsor determines it is in the best interest of the patient
- Patient non-compliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

4.6.2. Study Treatment Discontinuation

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

- Clinical deterioration (eg, uncontrollable pain secondary to disease or unmanageable ascites, etc.) attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status
- Intolerable toxicity related to tislelizumab, including development of an immune-mediated AE 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 anti-cancer therapy (see Section 4.4.2)
- Pregnancy

Patients will be permitted to continue study treatment after RECIST version 1.1 criteria for PD are met if they meet all of the following criteria:

- Absence of clinical symptoms and signs of disease progression (including clinically significant worsening laboratory values)
- Stable ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that necessitates urgent alternative medical intervention

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit.

The primary reason for study treatment discontinuation must be documented in the eCRF.

4.6.3. Study and Site Discontinuation

The sponsor has the right to terminate this study at any time. Reasons for terminating 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
- Patient enrollment is unsatisfactory

The sponsor will notify the investigator if the sponsor decides to discontinue the study. The sponsor has the right to close a site at any time. At the time of a site's closure, patients who are still on treatment may transfer to a long-term extension study for continuous treatment and monitoring when a long-term extension study becomes available. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice
- No study activity (ie, all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1. Safety Plan

Tislelizumab is not approved and is currently in clinical development. Human experience is currently limited and the entire safety profile is not known at this time. The following information is based on results from nonclinical and clinical studies and published data on similar molecules.

Measures will be taken to ensure the safety of patients participating in this trial, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2, respectively) and close monitoring (as indicated below and in Section 4.5). See Section 5.2 for complete details regarding safety reporting for this study.

Administration of tislelizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All AEs and SAEs will be recorded during the trial and for up to 30 days after the last dose of study treatment or until the initiation of another anti-cancer therapy, whichever occurs first. Immune-related AEs should be reported for 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. All drug related SAE will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or lost to follow up, whichever occurs first. Investigators are instructed to report all events (AEs, 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.

5.1.1. Risks Associated with Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral 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 Section 5.3.1.

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

5.1.2. General Plan to Manage Safety Concerns

5.1.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies 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 autoimmune conditions or with history of autoimmune disease that may relapse, and

patients who have received a live viral vaccine within 4 weeks before Cycle 1 Day 1 are excluded from the study (see Section 4.1).

5.1.2.2. Safety Data Review

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 1. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

All SAEs will be reported in an expedited fashion (see Section 5.2.7 and 5.2.9). In addition, the Medical Monitor will review and evaluate observed AEs on a regular basis.

All AEs will be recorded during the study (non-serious AE information will be collected from the time of the first dose of study drug and information on SAEs will be collected from the time of signed informed consent), and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first.

Immune-related AEs will be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

Patients who have an ongoing study treatment-related AE upon study completion or at discontinuation from the study 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.

5.1.3. Dose Interruption

There will be no dose reduction for tislelizumab in this study.

Dose delays or interruptions less than 12 weeks will be permitted. Investigators should make every effort to maintain dose intensity in patients.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drug and requires a dose to be withheld. The patients should resume tislelizumab treatment as soon as possible after the AEs recover to normal or Grade 1 within 12 weeks after last dose of study treatment. Two dosing delays due to toxicity will be permitted. In case a patient is benefiting from the study treatment while meeting the discontinuation criteria, discussion between the sponsor and investigator will be conducted to make a decision that will be in the best interest of the patient.

The tumor assessment schedule will not be altered if tislelizumab is delayed.

Management of tislelizumab irAEs is presented in Section 5.3.1. See Section 5.3.2 for guidelines for the management of infusion-related reactions.

5.2. Safety Parameters and Definitions

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.

5.2.1. Definition of an Adverse Event

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

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after investigational product 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 investigational product 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, and diagnostics reports) relative to the event. 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.

5.2.2. 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 event in which the patient was at risk of death at the time of the event. It does not refer to an event, 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 has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or

treatment that would not have been appropriate in the physician's office or out-patient 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 event by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to present 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

5.2.3. Suspected Unexpected Serious Adverse Reaction

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

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

5.2.4.1. 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 its relationship to study drug, will be reported until 30 days following their last dose of study treatment or initiation of new anticancer therapy, whichever comes first. Immune-related adverse events should be reported for 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. After treatment discontinuation, the investigator should report any SAEs that are believed to be related to tislelizumab treatment.

5.2.4.2. Following Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations 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 will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be re-sent to the sponsor within the time frames outlined in Section 5.2.7.1.

5.2.4.3. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, X-rays, 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 5.2.1) or an SAE (as defined in Section 5.2.2). This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessment that:

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

5.2.4.4. 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?

5.2.5. Evaluating Adverse Events and Serious Adverse Events

5.2.5.1. Assessment of Severity

The investigator will make assessment of severity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 4.03. 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
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 5.2.2.

5.2.5.2. 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 judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the tislelizumab IB 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.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc.) using the following definitions:

- Definitely related: There is clear evidence to suggest a causal relationship to the study drug, and there is reasonable temporal relationship; the occurrence of AE is definitely attributed to the pharmacological effect of study treatment.

- Probably related: There is a reasonable temporal relationship to suggest a causal relationship to the study drug; the occurrence of AE could not be explained by the patient's medical history, concurrent medical condition, or other the patient's signs or symptoms.
- Possibly related: There is some evidence to suggest a causal relationship to the study drug (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 such as the patient's clinical condition, other concomitant AEs.
- Unlikely related: There is little evidence to suggest there is a causal relationship to the study drug. There is another reasonable explanation for the AE such as disease or other drugs.
- Unrelated: An AE will be considered "not related" to the use of the study drug if any of the following criteria are met:
  - An unreasonable temporal relationship between administration of the drug and the onset on the AE (eg, the AE occurred either before, or too long after administration of the drug for it to be considered drug-related);
  - A causal relationship between the drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident);
  - A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

The causality for cases assessed with 5-point scale will be mapped to 2-point scale during aggregate safety data analysis according to the BeiGene latest mapping rule.

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

5.2.6.1. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. All SAEs and deaths regardless of relatedness to disease progression should be recorded and reported (see Section 5.2.7).

5.2.6.2. Death

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".

5.2.7. Reporting Serious Adverse Events

5.2.7.1. 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 3.

Table 3: Timeframe and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	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 event	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form or Pregnancy form

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

5.2.7.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 5.2.7.1. The SAE report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the sponsor within the designated timeframes. If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor of the SAE and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 5.2.5.2.

The sponsor will provide a list of project contacts for SAE receipt.

5.2.7.3. 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 5.2.7.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

All SUSARs (as defined in Section 5.2.3), will be submitted to all applicable regulatory authorities and investigators for tislelizumab studies.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements 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.

5.2.8. Pregnancy Reporting

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

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

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 investigational product should be recorded and reported as an SAE.

5.2.9. Post-study Adverse Event

A post-study AE or SAE is defined as any event that occurs outside of the AE/SAE reporting period, defined in Section 5.2.4.1.

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 event reasonably related to the investigational product, the investigator will promptly notify the sponsor.

5.2.10. 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 (RSI) documents:

- tislelizumab IB

5.3. 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.

5.3.1. Immune-related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related 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 6.

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 4. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on a recent European Society for Medical Oncology (ESMO) guideline (Haanen et al 2017) and American Society of Clinical Oncology (ASCO) guidelines (Brahmer et al 2018) and common immune-related toxicities are detailed in Appendix 6. For any AEs not included in Appendix 6, 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 4: 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.

Dose modification and management for irAEs are detailed in Appendix 6.

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

5.3.2. 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, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 5.

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

NCI-CTCAE Grade	Treatment Modification for tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 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 Event; NSAIDs, nonsteroidal anti-inflammatory drugs.

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

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

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

5.3.3. 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 ICU should be alerted for possible transfer if needed.

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

5.3.4. Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated glomerular filtration rate > 30 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study. The following algorithm is proposed for the use of steroid treatment in the management of irAEs:

- If the serum creatinine is normal at baseline, please see Section 5.3.1 and refer to Appendix 6 for diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with tislelizumab, refer to Appendix 6 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated glomerular filtration rate (GFR) using Appendix 7 and the estimated GFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the estimated GFR falls below 20 mL/min/1.73 m^2.
- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 6 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine

increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the sponsor medical monitor.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

6.1. Statistical Analysis

6.1.1. Analysis Sets

The Safety analysis set includes all patients who received any dose of tislelizumab.

The Efficacy Evaluable analysis set includes all patients who have received any dose of tislelizumab and had measurable disease per IRC according to RECIST version 1.1 at baseline. This will be the primary analysis set for the efficacy analyses.

The Per-Protocol (PP) analysis set includes patients in the Efficacy Evaluable analysis set who had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. This will be the secondary analysis set for efficacy analysis when there are over 15% patients, ie, 17 patients, who had major protocol deviations.

6.1.2. Patient Disposition

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

Protocol deviations will be summarized and listed by each category (major or minor).

6.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety analysis set using descriptive statistics. Continuous variables include age, weight, vital signs and time since initial UBC diagnosis; categorical variables include number of previous systemic regimens in the metastatic setting, gender, ECOG, country, race, smoking status, TNM staging, metastatic site, site of primary tumor and previous therapy with platinum-based regimen.

6.1.4. Prior and Concomitant Therapy

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 (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of

the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drug regardless of whether or not the patient starts a new anticancer therapy. A listing of prior and concomitant medications will be included in the CSR of this protocol.

6.2. Efficacy Analyses

6.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is ORR as determined by IRC using the RECIST version 1.1. ORR is defined as the proportion of patients achieving a best overall response of CR or PR.

The ORR in this study is estimated as 25%, which is deemed a clinically meaningful improvement based on a historical control of 10%. Hence, the null and alternative hypotheses are set as follows:

H_0: ORR=10%

Ha: ORR ≥25%

A binomial exact test will be performed for hypothesis testing among the evaluable patients (ie, patients with measurable disease at baseline) in the Efficacy Evaluable analysis set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the single agent tislelizumab statistically significantly increases ORR compared with historical control. Therefore, the superiority of single agent tislelizumab as measured by ORR will be demonstrated.

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

The primary efficacy analysis will be conducted no later than 6 months after the first dose of the last patient, and will be based on the Efficacy Evaluable analysis set. In case if patients without measurable disease per IRC who have been enrolled and treated, they will be excluded from the primary efficacy analysis.

6.2.2. Secondary Efficacy Analysis

DOR will be estimated using the Kaplan-Meier method. Its 95% CI will be constructed using Greenwood's formula. DOR censoring rule will follow US FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA Guidance 2007). Only patients who have achieved an objective response will be included in the analysis of DOR.

PFS and OS will be analyzed similarly as DOR in the Efficacy Evaluable analysis set. PFS at 12m and OS at 12m will be calculated based on KM method.

DCR will be summarized similarly as ORR in the Efficacy Evaluable analysis set.

Efficacy outcomes based on tumor assessment (ORR, DOR, PFS and DCR) per investigator review according to RECIST version 1.1 and irRECIST, respectively, will be summarized in the secondary efficacy analyses.

6.3. Safety Analysis

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v4.03. Laboratory values (eg, hematology, clinical chemistry, urinalysis), 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.

6.3.1. Extent of Exposure

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

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

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

6.3.2. Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 18.1 or higher) lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary System Organ Class (SOC) are also captured in the database.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 30 days following study drug discontinuation. The TEAE classification also applies to irAEs that are recorded up to 90 days after discontinuation from tislelizumab, 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 CTCAE v.4.03 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 definitely, possibly or probably 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, dose reduction, or dose delay will be summarized.

6.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included

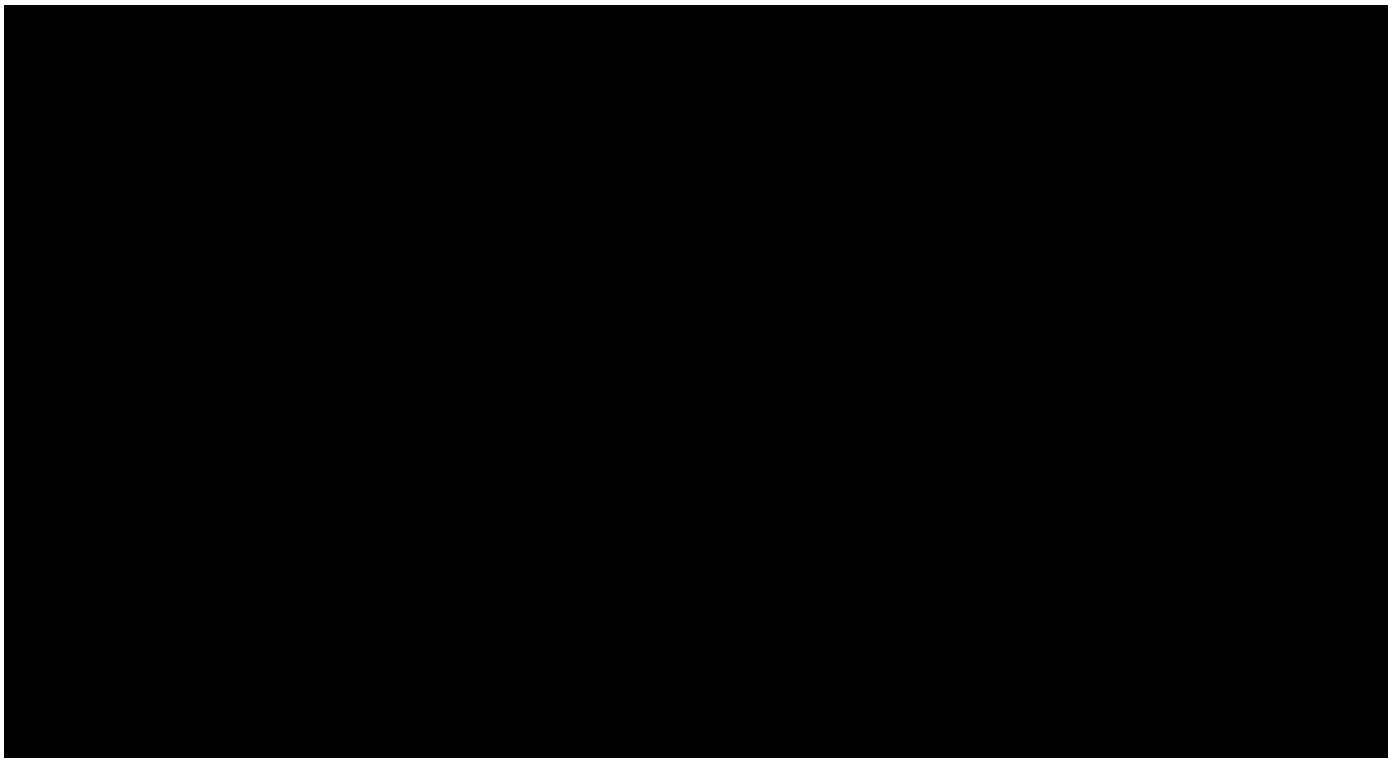
in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

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

6.3.4. Vital Signs

Specific vital signs (eg, blood pressure and temperature) will be summarized and listed. The change from baseline will also be displayed.

6.4. Exploratory Analyses



6.5. Determination of Sample Size

The sample size calculation was based on the power of the comparison between estimated ORR in the study and the historical rate. It is assumed an ORR of 25% in the study as compared to 10% in the historical control. Using a binomial exact text, the power is 0.986 with 110 patients to demonstrate statistical significance at a 1-sided alpha of 0.025.

6.6. Interim Analyses

No interim analysis for anti-tumor activity or efficacy is planned for this study.

7. DATA COLLECTION AND MANAGEMENT

7.1. Data Quality Assurance

The sponsor will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC) through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, sponsor or delegated contract research organization (CRO) will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The sponsor will perform oversight of the data management of this study. The sponsor or delegated CRO will produce an EDC study specification document that describes the quality review process to be performed on the data. Other electronic data will be sent directly to the sponsor or delegated CRO, using the sponsor's or delegated CRO's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the sponsor and records retention for the study data will be consistent with the sponsor's standard procedures.

7.2. Electronic Case Report Forms

eCRFs are to be completed using a sponsor-designated EDC system a validated data management system that is compliant with all regulatory requirements. Sites will receive training and help text for appropriate eCRF completion. eCRFs should be handled in accordance with instructions from the sponsor.

All eCRFs should be completed by designated, trained site staff. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. eCRFs should be reviewed and electronically signed and dated by the investigator or designated sub-investigator to attest to its accuracy, authenticity, and completeness.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

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

7.3. Source Data Documentation

Study monitors will perform ongoing source data verification to confirm that critical protocol data (ie, source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after

verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the study monitoring plan. This includes any protocol data to be entered directly into the eCRFs (ie, no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigator s and institutions must provide the sponsor and authorized study monitor direct access to applicable source documents and reports for trial-related monitoring, sponsor or delegated third party audits, and IRB/IEC review. The investigational site must also allow inspection by applicable health authorities.

7.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (ie, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data, as well as the reason for the change, name of the person making the change, and date of the change.

7.5. Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of investigational medicinal product including eCRFs, electronic patient-reported outcome data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the principal investigator for at least 15 years after completion or discontinuation of the study. 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 or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the sponsor. Written notification should be provided to the sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1. Compliance with Laws and Regulations

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

8.2. Informed Consent

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

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

The Consent Forms should 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 Consent Forms (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 Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

8.3. Institutional Review Board or Ethics Committee

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the 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 (see Section 9.5). In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug (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.

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.

8.4. Confidentiality

The sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any sponsor location.

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

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

Data generated by this study must be available for inspection upon request by representatives of the FDA, the China NMPA and other national and local health authorities, sponsor monitors, representatives, and collaborators, and the IRB/IEC for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from sponsor, including but not limited to the IB, this protocol, CRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

8.5. Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (ie, last patient, last visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1. Study Documentation

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/IEC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which include an audit trail containing a complete record of all changes to data.

9.2. Protocol Violations

The investigator should document and explain any violations from the approved protocol. The investigator should promptly report any violations that might impact patient safety and data integrity to the sponsor and to the IRB/IEC in accordance with established IRB/IEC policies and procedures.

9.3. Site Inspections

Site visits will be conducted by the sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4. Administrative Structure

This trial will be sponsored and managed by BeiGene (Shanghai) Co., Ltd. Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 30 sites in China and other Asian countries will participate to enroll approximately 110 patients.

Enrollment will occur through an IxRS system. Central facilities will be used for certain study assessments throughout the study (eg, specified laboratory tests, biomarker analyses, and PK analyses, and tumor imaging assessment) as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.5. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. Protocol amendments will be submitted to the IRB/IEC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/IEC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

9.6. Publication and Data Sharing Policy

A CSR 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 CSRs (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 regulator 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 Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2016).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The processes of reviewing manuscripts and presentations that are based on the data from this study is detailed in the investigator's clinical study agreement. 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.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening [1]	Treatment Cycles					Safety Follow-up [3]	Survival Follow-up [4]
		Cycles 1 to 3 (Every 21 days)			Cycle 4 and Subsequent Cycles (Every 21 Days)	End of Treatment Visit[2]		
Days (Window)	-28 to ~-1	1	8	15	1 (± 3)	0 to 7 Days	30 ± 7 Days After Last Dose	Every 3 Months
Informed consent [1]	x							
Inclusion/Exclusion criteria	x							
Demographic/Medical history/Prior medications [5]	x							
Concomitant medications [6]	x	x	x	x	x	x	x	
Adverse events [7]	x	x	x	x	x	x	x	x
Complete physical examination [8]	x						x	
Limited physical examination [8, 9]		x			x	x		
ECOG performance status [9]	x	x			x	x	x	
Vital signs [10]	x	x	x	x	x	x	x	
12-lead ECG [11]	x	As clinically indicated					x	
HBV and HCV serology [12]	x	As clinically indicated						
Hematology [9,13]	x [13]	x	x	x	x	x	x	
Serum chemistry [9,14]	x [14]	x	x	x	x	x	x	
Coagulation parameters [15]	x	As clinically indicated					x	
Urinalysis [9,16]	x	x			x		x	
Pregnancy test [17]	x	x			x	x	x	
Thyroid function [9,18]	x	x			x		x	
Anti-tislelizumab antibodies [19]		x			x		x	

Assessment	Screening [1]	Treatment Cycles					Safety Follow-up [3]	Survival Follow-up [4]
		Cycles 1 to 3 (Every 21 days)			Cycle 4 and Subsequent Cycles (Every 21 Days)	End of Treatment Visit[2]		
Days (Window)	-28 to ~-1	1	8	15	1 (± 3)	0 to 7 Days	30 ± 7 Days After Last Dose	Every 3 Months
Pharmacokinetics [20]		x			x		x	
Tumor assessment [21]	x				x	x		
Brain MRI/CT with contrast	x	As clinically indicated						
Study drug administration [22]		x			x			
Screening tumor tissue [23]	x							
Survival status [4]							x	x
Pulmonary function tests [24]	x							

Abbreviations: x, to be performed; ECOG, Eastern Cooperative Oncology Group; ECHO, echocardiography; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; TURBT, transurethral resection of bladder tumor

1. Written informed consent must be obtained before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to study entry may be used for screening assessments rather than repeating such tests.
2. The End of Treatment visit is conducted when the investigator determines that tislelizumab will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment visit, these tests need not be repeated. Tumor assessment is not required at the End of Treatment visit provided that fewer than 6 weeks have passed since the last assessment.
3. The mandatory safety follow-up visit is required to be conducted 30 days (±7 days) after the last dose of study therapy, or until initiation of a new anti-cancer therapy, whichever occurs first. Patients who are discontinued from the treatment due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) 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. The TEAE classification also applies to severe irAEs (≥ Grade 3 in severity by NCI-CTCAE) that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a new anticancer therapy.
4. Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits beginning 3 months after safety follow-up visit or as directed by sponsor and approximately every 3 months for the subsequent follow-ups until death, loss to follow-up, withdrawal of consent, or study termination by sponsor. All patients will be followed for survival and new anticancer therapy information unless the patient requests to be

withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study treatment but not from follow-up, the study staff may use a public information source (eg, county records) to obtain information about survival status only.

5. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
6. Concomitant medications include any prescription medications or over-the-counter medications. All concomitant medications received within 30 days before the first dose of study medication and 30 days after the last infusion of study medication should be recorded. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded. In addition, telephone contacts with patients should be conducted to assess immune-related adverse events (irAEs) and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days, and 90 days (± 14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy.
7. Adverse events and laboratory safety measurements will be graded per NCI-CTCAE version 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
8. Complete and limited physical examinations are defined in Section 4.5.3.
9. ECOG performance status, limited physical examination, and local laboratory assessments may be obtained ≤ 96 hours before Day 1 of each cycle.
10. Vital signs to include temperature, heart rate, and systolic and diastolic blood pressure. The patient's vital signs should be determined within 60 minutes before the infusion, and if clinically indicated during and 30 minutes after the infusion.
11. Electrocardiogram (ECG) recordings will be obtained during screening, safety follow-up and as clinically indicated at other timepoints. Patients should be resting and in a supine position for at least 10 minutes prior to ECG collection.
12. Testing will be performed by the local laboratory at screening and as clinically indicated. Include HBsAg, HBcAb and HCV antibody. Patients who are HBsAg positive or HCV antibody positive at screening must not be enrolled until further definite testing with HBV DNA titres < 500 IU/mL (or 2500 cps/mL), or HCV RNA polymerase chain reaction test is negative (lower than detection limit) respectively.
13. Hematology consists of complete blood count, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), and platelet count and will be analyzed by the local study site laboratory. A manual differential can be done if clinically indicated. Refer to Section 4.5.7 for a list of laboratory results obtained with 7 days prior to the first study treatment.
14. Serum chemistry includes blood urea nitrogen or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate (optional), calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, amylase, total protein, albumin, creatine kinase [CK], and creatine kinase cardiac muscle isoenzyme [CK-MB], and will be analyzed by the local study site laboratory. Refer to Section 4.5.7 for a list of laboratory results obtained with 7 days prior to the first study treatment. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead; if only either troponin is assessed per local standards that same should be evaluated throughout.

15. PT/INR and aPTT should be collected at screening and at the mandatory safety follow-up visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
16. Specific gravity, pH, glucose, protein, ketones, blood, and microscopic examination including WBC/HPF, RBC/HPF, and any additional findings.
17. Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to Cycle 1 Day 1. Urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
18. Analysis of free T3, free T4 and TSH will be performed by the local study site laboratory. Thyroid function tests will be performed on Day 1 of Cycle 1 and every three cycles thereafter (eg, Cycles 1, 4, 7, 10, etc.), and at the mandatory safety follow-up visit.
19. Blood for anti-tislelizumab antibodies should be collected within 60 min before start of Day 1 infusion of Cycle 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 C_{trough}. Analysis will be performed by a central laboratory.
20. Procedures for collection of PK samples are described in the laboratory manual. Predose (within 60 min before start infusion) samples should be collected at Day 1 of Cycle 1, 2, 5, 9 and 17; a postdose (within 30 min after the end of infusion) sample should be collected at Day 1 of Cycle 1 and Cycle 5; additional PK samples should be collected at the mandatory safety follow-up visit. Should a patient present with any Grade 3 or above immune-related adverse event, additional blood PK samples may be taken to determine the plasma concentration of tislelizumab.
21. Examinations performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1 Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. The same radiographic procedure must be used throughout the study for each patient. The investigator must review results before dosing at the next cycle. Patients will undergo tumor assessments every 9 weeks. Patients who discontinue from treatment for reasons other than disease progression (eg, toxicity) will continue scheduled tumor assessments until disease progression, withdrawal of consent, or death. Investigators may perform additional scans or more frequent assessments if clinically indicated. An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. It is recommended that the confirmatory tumor assessment is not left until the next scheduled CT scan, but be performed as soon as possible following the 28 days interval from the initial documentation of response. Tumor assessment will need to follow the original schedule after the confirmation scan. Patients who continue treatment beyond radiographic disease progression (see Section 4.6.2) will be monitored with a follow-up scan at least 4 weeks later or at the next regularly scheduled time point (not exceed 12 weeks) before discontinuation of study treatment.
22. The initial infusion will be delivered over 60 min; if well-tolerated, second infusion and each subsequent infusion may be administered over 30 min, which is the shortest time period permissible for infusion.
23. Representative tumor specimens in paraffin blocks (preferred) or around 15 unstained slides (at least 5 slides are required), with an associated pathology report, must be submitted for determination of sufficient viable tumor content prior to study enrollment; tumor specimens will be evaluated for PD-L1 expression and other biomarkers. Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. After signing of the Informed Consent Form, tumor tissue must be submitted up to 28 days prior to study entry for

evaluation. Patients who submit TURBT specimens that do not contain a muscle invasive component will be required to submit an additional specimen obtained at the time of cystectomy/nephroureterectomy or metastatic spread (ie, sample from a metastatic lesion).

24. Patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer will have pulmonary function testing which may including but is not limited to spirometry and assessment of diffusion capacity done during the screening period, to assist the determination of suitability for enrollment on the study.

APPENDIX 2. IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (IRRECIST)

RECIST v1.1 has its shortcomings for targeted immunotherapy in oncology. Using RECIST v1.1 in immunotherapy trials would lead to declaration of progressive disease (PD) too early, when the treatment effect is not yet fully evident. RECIST also neglects the importance of the 'flare effect' - pseudo-progression effect within the so-called flare time window.

Immune related Response Criteria (irRC) based on WHO criteria were published with an aim to provide better assessment of the effect of immunotherapeutic agents. With this poster we introduce irRECIST based on RECIST v1.1, irRC and Nishino 2013 findings. Our aim is to define criteria that better capture antitumor activity and reduce irRC criteria ambiguity (Bohnsack 2014).

The major differences between RECIST v1.1 (Eisenhauer 2009) and irRECIST are highlighted in table below:

	Summary of Key Changes	
	RECIST v1.1	**irRECIST**
New lesion after baseline	PD	New measurable lesions* are added to total measured tumor burden (TMTB)† and followed
Non-target lesions	May contribute to the designation of overall progression	Contribute mostly in the assessment of CR; only massive and unequivocal progression contributes to the assessments of other overall responses besides CR
Radiographic progression	≥20% increase in the sum of diameters; ≥1 new lesion; or unequivocal progression in non-target disease	≥20% increase in TMTB relative to baseline; or with massive and unequivocal progression of non-target lesions, even without progress in the TMTB

* Up to a maximum of five new lesions in total and a maximum of two new lesions per organ.
† Total Measured Tumor Burden of all target lesions

A guideline of irRECIST overall tumor assessment is summarized in table below:

% Change in TMTB Relative to Baseline	**Target Lesion Response**	**Non-Target Lesion[1] Response**	**New Measurable Lesions[2]**	**New Non-Measurable Lesions[3]**	**Overall Response**
100%↓[4]	CR	CR	No	No	irCR
100%↓[4]	CR	Non-CR or not all evaluated	No	No	irPR

% Change in TMTB Relative to Baseline	Target Lesion Response	Non-Target Lesion[1] Response	New Measurable Lesions[2]	New Non-Measurable Lesions[3]	Overall Response
>30%↓	PR	Non-PD[5]	Yes/No	Yes/No	irPR
Between 30%↓and 20%↑	SD	Non-PD[5]	Yes/No	Yes/No	irSD
N/A in this study					irNN
≥20%↑	PD	Any	Yes/No	Yes/No	irPD
Not all evaluated	NE	Non-PD[5]	Yes/No	Yes/No	irNE
N/A in this study					irND

1. Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.
2. ≤ 2 lesions per organ, ≤ 5 lesions total, per timepoint.
3. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new non-measurable lesions prevent irCR.
4. When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.
5. PD indicates a massive and unequivocal progression of non-target lesions.

The text below was obtained from the reference: Bohnsack O, Hoos A, and Ludajic K. Adaptation of the immune related response criteria: irRECIST. Annals of Oncology. 2014.25 (suppl_4): iv361-iv372 (Bohnsack 2014)

Original irRC Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.	**1. 0 Baseline: Measurable Lesion Definitions and Target Lesion Selection** Follow the definitions from RECIST v1.1. Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for nonnodal lesions and ≥15 mm in short axis for nodal lesions • 10 mm caliper measurement by clinical exam • 20 mm by chest X-ray	Up to 5 target lesions may be selected at baseline. Lesions will be measured unidimensionally. The minimum target lesion size at baseline in irRECIST is aligned with RECIST v1.1, as outlined in Nishino 2013.
WHO 5.1.2 Unmeasurable Disease There are many forms of unmeasurable disease, and only a few are mentioned as	**1.1. Baseline: Non-measurable Lesion Definitions** Follow the definitions from RECIST v1.1 Non-target lesions will include: • Measurable lesions not selected as target lesions	Although irRC does not specifically define non-target lesions, irRC is derived from WHO criteria and indicates accordance with the same for the purposes of definitions of

Original irRC Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
examples: 1. Lymphangitic pulmonary metastases. 2. Skin involvement in breast cancer. 3. Abdominal masses that can be palpated but not measured.	• All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), ie. the longest per-pendicular diameter is≥10 and < 15 mm. • Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.	non-target lesions. Further clarifications in alignment with RECIST v1.1 are provided.
Not specified.	**1.2 Baseline: Target and Non-Target Lymph Node Lesion Definitions** Follow the definitions from RECIST v1.1	No change in definition of target and non-target lymph nodes from RECIST v1.1.
Not specified.	**1.3 Baseline: Non-Target Lesion Selection** All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.	In alignment with RECIST v1.1, all malignant lesions have to be selected at baseline. The excess of measurable lesions and all true non-measurable lesions will be selected as non-target lesions at baseline and followed at subsequent timepoints.
Not specified.	**1.4 Baseline: Bone Lesions** Follow the definitions from RECIST v1.1. Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.	Bone lesions are to be handled the same as in RECIST v1.1.
Not specified.	**1.5 Baseline: Brain Lesions** Brain Lesions detected on brain scans can be considered as both target or non-target lesions.	Brain lesions can be selected as target or non-target lesions at baseline, depending on the protocol definition, indication, and study design.
Not specified.	**1.6 Baseline: Cystic and Necrotic Lesions as Target Lesions** Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.	RECIST v1.1 does not integrate viability of tumor tissue into the assessment, and that is carried over into irRECIST.
Not specified.	**1.7 Baseline: Lesions with Prior Local Treatment** During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (eg, previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.	In order to minimize site vs. central discrepancy information about prior intervention needs to be available to both the Investigators and independent reviewers.
Not specified.	**1.8 Baseline: No Disease at Baseline** If a patient has no measurable and no non-measurable disease at baseline the radiologist will	irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow

Original irRC Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
	assign'No Disease' (irND) as the overall tumor assessment for any available follow-up timepoints unless new measurable lesions are identified and contribute to the TMTB.	to include patients with no visible disease. This had not been addressed at all in any prior immune-response related criteria but needs to be included to also allow for these patients to be assessed accurately.
At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥5×5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden.	**2.0 Follow-up: Recording of Target and New Measureable Lesion Measurements** The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the Total Measured Tumor Burden (TMTB) at follow-up.	In alignment with Nishino et al 2013, unidimensional measurements are used. Measurements of all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into TMTB at follow-up.
	2.1 Follow-up: Definition of Measurable New Lesions In order to be selected as new measurable lesions (≤2 lesions per organ, ≤5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.	Proposed selection of up to 5 new measurable lesions of at least 10 mm each verus 10 new measurable lesions as suggested in the irRC criteria is due to the following: 5 new measurable lesions add up at least 50 mm to the TMTB. Since PD is determined by at least a 20% increase in TMTB compared to nadir, this would mean that for irPD assessment the nadir TMTB had to be 25 cm, or 10 cm for 2 lesions in one organ, which is a significant tumor burden already for any cancer patient. That is why measuring up to 5 new lesions in total is sufficient and will not obstruct an irPD assessment. Measuring more than 5 new lesons is not needed. Larger lesions must be preferred as new measurable over smaller lesions, because there will be a greater impact of the TMTB %-increase by these larger lesions for irPD, to support a most conservative approach.
Non-index lesions at follow-up timepoints contribute to defining irCR (complete disappearance required).	**2.2 Follow-up: Non-Target Lesion Assessment** The RECIST v1.1 definitions for the assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.	Non-target lesions have a subordinate function. In the event that non-target lesions massively progress one cannot ignore such worsening and in these rare cases irPD based only on non-target lesions will be a valid assessment option.
New, non-measurable lesions at follow-up timepoints do not define progression, they only preclude irCR.	**2.3 Follow-up: New Non-Measurable Lesions Definition and Assessment** All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and	When new non-measurable lesions substantially worsen in these rare cases irPD based only on new non-measurable lesions will be an assessment option.

Original irRC Including WHO Criteria References	irRECIST Modifications and Clarifications	Rationale for Modification
	unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the timepoint. Persisting new nonmeasurable lesions prevent irCR.	
irRC Overall Tumor Assessments **irCR,** complete disappearance of all lesions (whether measurable or not, and no new lesions) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented **irPR,** decrease in tumor burden ≥50% relative to baseline • Confirmed by a consecutive assessment at least 4 weeks after first documentation **irSD,** not meeting criteria for irCR or irPR, in absence of irPD **irPD,** increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) • Confirmation by a repeat, consecutive assessment no less than 4 weeks from the	**2.4 irRC Overall Tumor Assessments** **irCR,** complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory. **irPR**, decrease of ≥30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions. **irSD,** failure to meet criteria for irCR or irPR in the absence of irPD. **irNN,** no target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD. **irPD,** minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. **irNE,** used in exceptional cases where insufficient data exists. **irND,** in adjuvant setting when no disease is detected.	The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions. The thresholds for irPR and irPD assessment are aligned with RECIST v1.1, and confirmation of response is not required. An irPD confirmation scan may be recommended for patients with a minimal TMTB%-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response.

APPENDIX 3. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer 2009; 45:228 24729 (Eisenhauer 2009).

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

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

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

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

Bone lesions:

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

- Blastic bone lesions are non-measurable
- Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Lesions with prior local treatment:
- Tumor lesions situated in a previously irradiated area, or in an area patented to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable

Target Lesions

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

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

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being

"too small to measure". When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

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

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease. In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the

change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

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

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease.

Note:

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation

may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 4. PRE-EXISTING AUTOIMMUNE DISEASES

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (eg, acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

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 pemphigold	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn's disease
Dermatomyositis	Diabetes mellitus Type 1
Dysautonomia	Epidermolysis bullosa acquista
Gestational pemphigoid	Giant cell arteritis
Goodpasture's syndrome	Graves' disease
Guillain-Barré syndrome	Hashimoto's disease
IgA nephropathy	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
Scleroderma	Sjögren's syndrome
Stiff-Person syndrome	Takayasu's arteritis
Ulcerative colitis	Vogt-Kovanagi-Harada disease
Granulomatosis with polyangiitis	

APPENDIX 5. 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 6. 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.

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If 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.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; 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 cystolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance

imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-related Adverse Events

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

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
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.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	or > 3X-6X ULN	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.	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.
	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	Initiate IV (methyl)prednisolone	Discontinue study

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	complications or dehydration	not contraindicated by infection.	
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	**< 2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion		
	3 Severe symptoms with mild 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.	
	4 Life-threatening		

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

APPENDIX 7. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating GFR from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation1 and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable. Read more about creatinine standardization.

This CKD-EPI equation calculator should be used when Scr reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

GFR = 141 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of Scr /κ or 1, and

max indicates the maximum of Scr /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfr-calculators.aspx

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