CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of BGB-A317 (Anti−PD1 Antibody) Compared with Docetaxel in Patients with Non−Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen
Protocol Identifier:	BGB-A317-303
Phase:	3
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Treatment of Non−Small Cell Lung Cancer in the second- or third-line setting
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, California 94403 USA BeiGene (Shanghai) Co., Ltd.* Floor 4, Building D No. 780, Cailun Road Pilot Free Trade Zone Shanghai 201203, China * BeiGene (Shanghai) Co., Ltd., is China sponsor for the study.
Reference Number	EudraCT 2018-000245-39
Sponsor Medical Monitors	[redacted] 22nd Floor, Tower D Central International Trade Center 6A Jianguomenwai Avenue, Chaoyang District Beijing 100022, China Email: [redacted] Phone: [redacted] [redacted] 22nd Floor, Tower D Central International Trade Center 6A Jianguomenwai Avenue, Chaoyang District Beijing 100022, China Email: [redacted] Phone: [redacted] [redacted] 55 Challenger Road, Suite 501, Ridgefield Park New Jersey 07660, USA Email: [redacted] Phone: [redacted]
NCT Number:	NCT03358875

Original Protocol:	12 July 2017
Amendment 1.0:	14 February 2018
Amendment 2.0:	20 July 2018
Amendment 3.0:	09 March 2020

FINAL PROTOCOL APPROVAL SHEET

Title: A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of BGB-A317 (Anti–PD1 Antibody) Compared with Docetaxel in Patients with Non–Small Cell Lung Cancer Who Have Progressed on a Prior Platinum-Containing Regimen

BeiGene, Ltd. Approval:

[redacted]

9th Mar 2020

Medical Monitor

Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-303

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read the protocol in its entirety and agree to conduct the study accordingly.

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

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SYNOPSIS

Name of Sponsor: BeiGene (Shanghai) Co., Ltd.

Investigational Product: Tislelizumab (BGB-A317)

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Protocol Identifier: BGB-A317-303

Phase of Development: 3

Planned Number of Patients: Approximately 800

Study Centers: Approximately 40 centers in Asia Pacific countries and approximately 60 to 80 centers in approximately 15 other countries

Study Objectives:

Primary:

- To compare the efficacy, as measured by overall survival (OS), of tislelizumab with docetaxel in the second- or third-line setting in patients with non-small cell lung cancer (NSCLC) who have progressed on a prior platinum-containing regimen. A comparison of the treatment arms will be performed in:
    - The intent-to-treat (ITT) Analysis Set
    - The programmed cell death protein ligand-1 (PD-L1) positive Analysis Set, where PD-L1 positive is defined as ≥25% of tumor cells (TCs) with PD-L1 membrane staining via the Ventana SP263 assay

Secondary:

- To compare the efficacy of tislelizumab and docetaxel as measured by objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in:
    - The ITT Analysis Set
    - The PD-L1 positive Analysis Set
- To compare health-related quality of life (HRQoL) between tislelizumab and docetaxel arms
- To evaluate the safety and tolerability of tislelizumab versus docetaxel

Exploratory:

- To compare tumor assessment outcomes (ie, disease control rate [DCR] and clinical benefit rate [CBR]) between tislelizumab and docetaxel assessed by investigator per RECIST v1.1
- To explore potential predictive biomarkers for efficacy including but not limited to PD-L1 expression, tumor mutational burden (TMB), gene expression profile (GEP), and tumor-infiltrating immune cells
- To characterize the pharmacokinetics (PK) of tislelizumab in patients with NSCLC
- To determine host immunogenicity to tislelizumab in patients with NSCLC

Study Endpoints:

Primary:

- OS – defined as the time from the date of randomization to the date of death due to any cause in the ITT and PD-L1 positive Analysis Set

Secondary:

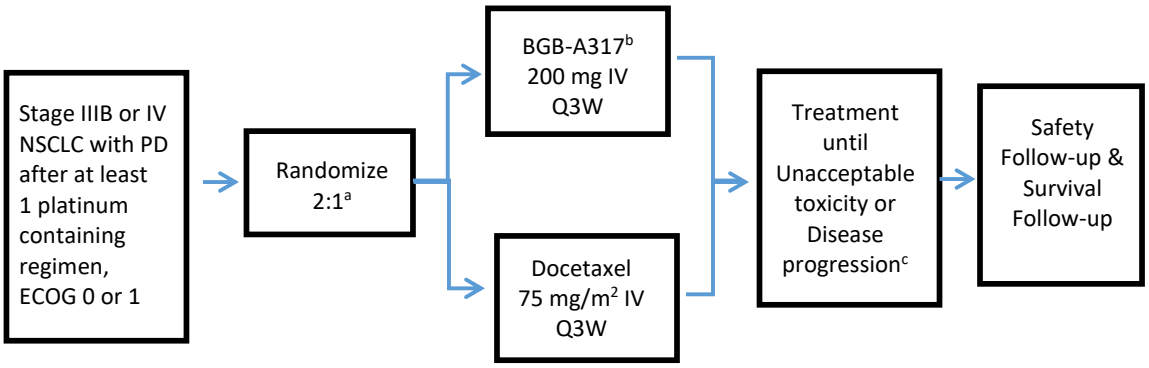
- ORR – defined as the proportion of patients in the ITT and PD-L1 positive Analysis Set who had a complete response (CR) or partial response (PR) as assessed by the investigator per RECIST v1.1
- DoR – defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator per RECIST v1.1, or death from any cause, whichever comes first in the ITT and PD-L1 positive Analysis Set
- PFS – defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurs first, in the ITT and PD-L1 positive Analysis Set
- HRQoL – measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ-LC13), Core 30 (EORTC QLQ-C30), and European Quality of Life 5-Dimensions, 5-level (EQ-5D-5L) scale
- Incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4.03

Exploratory:

- DCR – defined as the proportion of patients whose best overall response (BOR) is CR, PR or stable disease (SD) per RECIST v1.1
- CBR - defined as the proportion of patients who have CR, PR and SD that is ≥24 weeks in duration per RECIST v1.1
- PD-L1 expression, TMB, GEP, and tumor-infiltrating immune cells as predictive biomarkers for response
- Summary of serum concentrations of tislelizumab in the pharmacokinetic Analysis Set
- Assessments of immunogenicity of tislelizumab by determining the incidence of anti-drug antibodies (ADAs) in the ADA Analysis Set

Study Design:

This is a randomized, open-label multicenter Phase 3 study designed to compare the efficacy and safety of tislelizumab versus docetaxel as treatment in the second- or third-line setting in patients with NSCLC. The primary endpoint of the study is measured by OS in both the ITT and PD-L1 positive Analysis Sets.



Abbreviations: BGB-A317 = tislelizumab; BID = twice daily; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; NSCLC = Non-small cell lung cancer; PD = progressive disease; Q3W = once every 3 weeks, TC = tumor cells.

a. Randomization will be stratified by histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).
b. The initial infusion (Cycle 1, Day 1) will be administered over a period of 60 minutes. If this infusion is well tolerated, subsequent infusions may be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for a period of at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post infusion monitoring period of ≥ 30 minutes will be required.
c. At the discretion of the investigator, patients in the tislelizumab arm may be treated beyond disease progression under protocol-defined conditions (Section 7.5).

Patients must have histologically confirmed, locally advanced or metastatic NSCLC (squamous or non-squamous). Histology of NSCLC (squamous or non-squamous) will be confirmed at the investigator's site. Patients with known epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement are ineligible for the study. Documentation of wild type EGFR by tissue-based test is required for non-squamous patients to enter the study. Archival tumor tissues (not restricted to pretreatment) will be collected for biomarker analysis at a central laboratory. If archived formalin-fixed paraffin-embedded (FFPE) tissue is not sufficient, a fresh biopsy sample will be mandatory.

Patients must have been treated with at least one platinum-containing regimen but not more than 2 prior lines of systemic chemotherapy and have disease progression during or following chemotherapy treatment. Patients who progressed or have disease recurrence during or after neo-adjuvant or adjuvant therapy with platinum-containing regimen (counted as one line of therapy) within 6 months are eligible to enroll into the study.

After signing an informed consent form and screening for eligibility, patients will be randomized in a 2:1 ratio to receive tislelizumab or docetaxel in the following 2 arms:

Arm A: Tislelizumab 200 mg intravenously (IV) once every 3 weeks

Arm B: Docetaxel 75 mg/m^2 IV once every 3 weeks

Randomization will be 2:1 (Arm A:Arm B) stratified by histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).

Administration of docetaxel and tislelizumab will continue until disease progression, as assessed by investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first. Patients receiving tislelizumab will be permitted to continue tislelizumab treatment beyond radio-imaging progression if clinical benefit is seen in the absence of symptomatic deterioration and unacceptable toxicity per investigator's discretion.

Study Assessments:

Tumor response will be evaluated by investigators every 9 weeks (± 7 days) during Year 1 and every 12 weeks (± 7 days) from Year 2 onwards based on RECIST v1.1. If a patient discontinues study treatment due to reasons other than disease progression, then tumor assessments should continue to be performed as scheduled until the start of new anticancer therapy, disease progression, death, loss to follow-up, or withdrawn consent. Any new anticancer therapy after discontinuation of study treatment from both arms will be documented.

To determine the PK properties of tislelizumab and host immunogenic response to tislelizumab, blood samples will be collected at various time points as outlined in Appendix 1.

Patients will be evaluated for adverse events (AEs) and serious adverse events (SAEs) occurring up to 30 days after the last dose of either study drug or initiation of new anticancer therapy, whichever occurs first, (all severity grades according to NCI-CTCAE v4.03) and all immune-related AEs (irAEs) (tislelizumab arm only) occurring up to 90 days after the last dose of tislelizumab, 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.

Duration of Patient Participation:

Total duration of study participation will vary by patient.

Study Population:

Patients with locally advanced or metastatic non−small cell lung cancer with disease progression during or following treatment with at least one prior platinum-containing regimen.

Key Eligibility Criteria:

The population under study is adult patients (≥ 18 years of age on the day the patient voluntarily agrees to participate in the study) with locally advanced or metastatic (Stage IIIB or IV) NSCLC with disease progression during or following treatment with at least one platinum-containing regimen. Patients with known EGFR sensitizing or driver mutation or ALK rearrangement are ineligible for the study. For patients with non-squamous NSCLC, documentation of wild type EGFR by tissue-based test is required to enter the study. For patients without documented wild type EGFR, fresh or archival tumor tissues (FFPE blocks or 6 freshly cut unstained FFPE slides) are required for central EGFR mutation assessment. In addition, all patients are required to have fresh or archival tumor tissues (FFPE blocks or approximately 11 [a minimum of 5] freshly cut unstained FFPE slides for biomarker analysis including PD-L1 expression, have adequate hematologic and end-organ function, and an Eastern Cooperative Oncology Group Performance Status score of ≤1.

Test Product, Dose and Mode of Administration:

Tislelizumab will be administered at a dose of 200 mg IV once every 3 weeks

Reference Therapy, Dose, and Mode of Administration:

Docetaxel will be administered at a dose of 75 mg/m^2 IV once every 3 weeks

Statistical Methods:

This trial was originally designed to enroll patients from China and Asia Pacific (CAP) region. After amendment 1, it has been expanded to enroll patients from the rest of the world (ROW) as well. The primary and secondary objectives of the trial have not been changed due to this expansion. As of amendment 3.0, the number of death events that triggers interim analysis has been changed to 426 (approximately 76% of total number of 560 deaths) in the ITT Analysis Set. All analyses and testing discussed in Section 9 pertaining to study Analysis Set include both the CAP and ROW regions of patients.

Statistical Analysis:

The overall type I error will be strongly controlled at a one-sided α of 0.025 within the 2 dual primary hypotheses and 4 secondary efficacy hypotheses. Initially, α of 0.02 and 0.007 will be assigned to the primary hypothesis testing in the ITT and PD-L1 positive Analysis Sets, respectively. The α allocation accounts for the positive correlation between the test statistics in the 2 Analysis Sets (ie, PD-L1 positive is a subset of the ITT Analysis Set). The overall type I error is controlled at 0.025 when at least 30% of the deaths in the ITT Analysis Set are from the PD-L1 positive subset. The α of 0.007 in the PD-L1 testing will be adjusted downwards if the final observed percentage is lower. When the trial proceeds to the final analysis, the OS hypothesis in the ITT Analysis Set will be tested first.

If the OS hypothesis in ITT Analysis Set is rejected, the unused α will be passed on to the OS hypothesis test in the PD-L1 positive Analysis Set; followed by the second efficacy hypothesis testing in the sequential order of ORR in the PD-L1 positive Analysis Set, DoR in the PD-L1 positive Analysis Set, PFS in the PD-L1 positive Analysis Set, PFS in the ITT Analysis Set, ORR in the ITT Analysis Set, DoR in the ITT Analysis Set, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/Quality of Life (QoL) in the ITT and PD-L1 Analysis Sets. Otherwise, if the OS hypothesis in the ITT Analysis Set cannot be rejected, hypothesis testing will be carried out sequentially only in the PD-L1 positive Analysis Set for OS, ORR, DoR, PFS, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/QoL scale at α of 0.007. The testing will continue until the first non-significant outcome occurs following the methodology of Glimm et al (2010).

Analysis Sets:

- The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arms. This will be the primary Analysis Set for efficacy analysis. The ITT Analysis Set will be summarized for both the China and Asia Pacific (ITT-CAP) Analysis Set and the rest of world (ITT-ROW) Analysis Set.
- The PD-L1 positive Analysis Set (≥25% of TC with PD-L1 membrane staining) includes all randomized patients whose tumors were PD-L1 positive. Patients will be analyzed according to their randomized treatment arms. This will be the dual primary analysis population for efficacy analysis.
- Safety Analysis Set includes all patients who received at least one dose of study drug. It will be the population for the safety analyses.
- The PK Analysis Set includes patients who contributed at least one quantifiable postdose PK sample.
- The ADA Analysis Set includes all patients who have received at least 1 dose of tislelizumab for whom non-missing baseline ADA and at least 1 non-missing postbaseline ADA results are available.

Primary Efficacy Analysis:

Overall Survival

OS in ITT Analysis Set:

OS will be compared between tislelizumab (Arm A) and docetaxel (Arm B) in a stratified log-rank test using a significance level of 0.02 (one-sided).

The null hypothesis to be tested is:

H_0: OS in Arm A = OS in Arm B

against the alternative hypothesis:

H_a: OS in Arm A $\neq$ OS in Arm B

This will be the primary analysis once the targeted numbers of deaths are reached in the ITT Analysis Set.

The p-value from a stratified log-rank test will be presented using stratification factors.

The median OS and the cumulative probability of OS at every 6 months if estimable, will be calculated for each treatment arm and presented with two-sided 95% confidence intervals (CIs). Kaplan-Meier (KM) survival probabilities for each arm will be plotted over time.

The hazard ratio (HR) between tislelizumab and docetaxel ($HR_{A/B}$) and its 95% CI will be estimated using a Cox proportional hazard model with treatment arm as a factor and stratified by the actual value of the stratification factors.

OS in the PD-L1 Positive Analysis Set:

The hypothesis testing of OS in the PD-L1 positive Analysis Set will be carried out at a significance level of 0.007. If the OS hypothesis in the ITT Analysis Set is rejected, its corresponding α will be shifted to the testing in the PD-L1 positive Analysis Set (ie a total α of 0.025). Similar statistical methods as described above will be applied with histology and line of therapy as strata in the stratified analyses.

Timing and Stopping Boundary in the Interim and Final Analyses of OS:

There will be one interim analysis of OS performed in the ITT Analysis Set. The interim analysis will be performed when approximately 426 deaths (76% of the target number of 560 deaths) among the 2 treatment arms are observed in the ITT Analysis Set. It is estimated that it will take approximately 23.1 months to observe 426 events. The final analysis of OS will take place after 560 and 207 deaths are observed in the ITT Analysis Set and its subgroup of patients with positive PD-L1 tumors, respectively. Thus, the predefined number of deaths in the ITT Analysis Set will trigger the interim and final analyses. The information fraction used in α spending function will be based on the observed number of deaths in the ITT Analysis Set at the corresponding time points. A Hwang-Shih-DeCani spending function with γ parameter of -2 will be used in setting up the upper (efficacy) boundary. Stopping boundaries (p-value and Z score) of superiority test for OS at the interim and final analyses in the ITT Analysis Set, as well as OS at the final analysis in the PD-L1 positive Analysis Set are shown in the table below. The boundaries of hypothesis testing in OS will be updated according to the actual numbers of death events in the interim and final analyses, using the pre-specified α spending function.

Stopping Boundaries (in Terms of P-value and Z Score) and Approximate HR Threshold of Interim and Final Analyses of OS

	Time (months)	# Deaths	p-value (Z score) for Efficacy	Approximate HR Threshold for Efficacy
Interim analysis in ITT	23.1	426	<0.0112 (>2.28)	<0.791
Final analysis in ITT	31.0	560	<0.0153 (>2.16)	<0.824
Final analysis in PD-L1 positive	31.0	207	<0.007 (>2.46)	<0.696

Abbreviations: HR = hazard ratio; ITT = intent-to-treat (Analysis Set); PD-L1 – programmed cell death protein ligand 1

Secondary Efficacy Analysis:

The statistical significance of the difference in ORR between arms in the ITT Analysis Set will be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

The PFS will be compared between 2 arms in the ITT Analysis Set using a stratified log-rank test using actual stratification factors as strata.

The median PFS and the cumulative probability of PFS at every 3 months will be calculated for each treatment arm and presented with two-sided 95% CIs. PFS will be estimated using the Kaplan-Meier method. The PFS censoring rule will follow the Food and Drug Administration (FDA) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

DoR will be analyzed similarly as PFS. It will be summarized within responders.

Efficacy outcomes (ie, ORR, DoR, and PFS) in the PD-L1 positive Analysis Set will be summarized similarly.

EORTC QLQ-LC13, EORTC QLQ-C30, and EQ-5D-5L post-baseline scores will be compared between the 2 treatment arms, using a mixed model. In addition, changes from baseline in global health status/QoL of QLQ-C30 and the functional and symptom scales of QLQ-C30, QLQ-LC13 and EQ-5D-5L (descriptive scores and visual analog scales) will be summarized descriptively.

Exploratory Efficacy Analysis:

Exploratory efficacy endpoints assessed by investigator per RECIST v1.1, including DCR, and CBR, will be analyzed in the exploratory analysis.

BOR will be defined as the best response recorded from start of study drug until data cut or start of new anticancer treatment. Patients with no postbaseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and progressive disease [PD]) will be presented by treatment arm.

DCR and CBR will be analyzed similarly as ORR in the ITT and PD-L1 positive Analysis Sets.

Analysis of the relationship of response to exploratory biomarker expression (eg, PD-L1 expression) may be carried out.

Safety Analysis:

Drug exposure will be summarized as number of cycles received, duration, dosage, and dose intensity by treatment arm.

Verbatim description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA®) terms and graded per NCI-CTCAE v.4.03. All TEAEs will be summarized. A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy. TEAEs also includes all irAEs and drug-related SAEs recorded up to 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

The SAEs, deaths, irAEs, TEAEs of Grade 3 or above, treatment related TEAE and TEAEs that led to treatment discontinuation, dose interruption dose reduction, or dose delay will be summarized. Multiple grades of the same event will be counted once per patient at the maximum severity within a System Organ Class (SOC) and Preferred Term (PT).

Clinical laboratory data with values outside of the normal ranges will be identified. Select laboratory data will be summarized by NIC-CTCAE grade. Vital signs will also be summarized.

Pharmacokinetic Analysis:

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

Tislelizumab serum concentration data, including but not limited to minimum observed plasma concentration (C_{trough}) will be tabulated and summarized for each cycle at which PK are to be measured. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK analyses will be conducted as appropriate.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

Immunogenicity Analysis:

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

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

Sample Size Considerations:

The original sample size calculation (ie, approximately 640 patients in China and Asia Pacific region) is based on the number of events required to demonstrate the OS superiority of Arm A to Arm B in ITT-CAP and ITT-CAP patients with PD-L1 positive tumors. The sample size has been increased to include an additional 160 patients from ROW hence a total of approximately 800 patients will be recruited into the trial.

Six hundred and forty patients in ITT-CAP will be enrolled over a 16-month period at a constant enrollment rate and randomized in a 2:1 ratio to Arms A and B. The enrollment of 160 patients in ITT-ROW is expected to start approximately 8 months after that for the ITT-CAP and to last about 12 months. The median OS is assumed as 10 months in Arm B.

An interim analysis is planned when approximately 426 deaths in the ITT Analysis Set have been observed, which represents 76% of the planned number of events (ie 560) in the ITT for the final analysis. There is an approximately 87% power to detect an OS HR (Arm A/Arm B) of 0.75 with a one-sided type I error of 0.02 in the ITT.

A Hwang-Shih-DeCani spending function with γ parameter of -2 based on the information fraction in the ITT Analysis Set is used in setting up the upper (efficacy) boundary. The stopping boundaries in

Table 10 will be updated based on the actual death events observed in the ITT Analysis Set at the interim and final analyses.

The superiority test of OS in the PD-L1 positive Analysis Set will be performed only in the final analysis. Two hundred and seven deaths in the ITT patients with PD-L1 positive tumors are required to have approximately 86% power to detect an OS HR of 0.60 with a one-sided type I error of 0.007. Assuming the prevalence of PD-L1 positivity is 40% in the ITT Analysis Set, it will take approximately 31.0 months to accumulate the required approximately 207 events in approximately 320 patients with PD-L1 positive tumors in the ITT Analysis Set.

The PD-L1 expression status will be closely monitored and enrollment of patients whose tumors are PD-L1 negative will be stopped as necessary through Interactive web response technology upon reaching ~60%, that is to ensure that the percentage of PD-L1 positive patients is no less than 40% of the ITT Analysis Set. The capping of PD-L1 negative patients to ~60% will be implemented in both ITT-CAP and ITT-ROW independently.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Antidrug antibody
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
BGB-A317	Code name for Monoclonal Antibody tislelizumab
BOR	Best overall response
BSC	Best supportive care
CAP	China Asia Pacific cohort
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CNS	Central nervous System
CR	Complete response
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
EGFR	Epidermal growth factor receptor
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	5-level version of European Quality of Life 5-Dimensional Questionnaire

Abbreviation	Definition
Fc	Fragment crystallizable region (typically, of immunoglobulin G)
FcγR	Gamma Fc receptor, such as Fcγ-RI, Fcγ-RIII, etc.
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
GEP	Gene expression profile
GFR	Glomerular filtration rate
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
$HR_{A/B}$	Hazard ratio between tislelizumab and docetaxel
HRQoL	Health-related quality of life
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG4	Immunoglobulin G4
IND	Investigational New Drug
irAE	Immune-related adverse event
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous(ly)
IWRT	Interactive web response technology
K_D	Dissociation constant
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Objective response rate

Abbreviation	Definition
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed cell death protein ligand-1
PD-L2	Programmed cell death protein ligand -2
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PS	Performance status
PT	Preferred term
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
ROS1	ROS proto-oncogene 1
ROW	Rest of world cohort
SAE	Serious adverse event
SD	Stable disease (or standard deviation in statistical sections)
SCLC	Small cell lung cancer
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse events
$T_{1/2}$	Terminal elimination half-life
TC	Tumor cells
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TMB	Tumor mutational burden
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

1. INTRODUCTION

1.1. Lung Cancer

Lung cancer has been the most common cancer worldwide for many decades. In 2012, there were an estimated 1.8 million new diagnoses of lung cancer worldwide, representing 12.7% of all new cancers. It is also the most common of cancer-related deaths, with 1.59 million deaths worldwide, corresponding to 18.2% of total deaths (GLOBOCAN, 2012). Among all lung cancer cases, 605,900 or 35.8% of new cases were in China, and 486,600 or 37.6% of lung cancer-related deaths were in China. Lung cancer is the most common cancer and leading cause of cancer-related death in both males and females, with increasing incidences in both males and females during the past decades. A recent publication indicates there were 733,300 new cases and 610,200 deaths from lung cancer in 2015 (Chen et al, 2016). The risk for lung cancer is higher in males than females (2.27:1) (Chen and Zou, 2010).

The major histological types of lung cancer are non-small cell lung cancer (NSCLC), the most common type; small cell lung cancer (SCLC), the second most common type; and lung carcinoid tumors. NSCLC accounts for 80% to 85% of all lung cancers and originates from the epithelial cells of the lung with the following major histological subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma (PDQ Adult Treatment Editorial Board, 2017). The SCLCs account for approximately 10% to 15% of all lung cancers (PDQ Adult Treatment Editorial Board, 2017).

The prognosis for lung cancer patients is relatively poor. However, the prognosis depends greatly on the stage at which the cancer is detected. Currently, lung cancer staging is performed worldwide according to the 7th edition of tumor, node, metastasis (TNM) Classification of Malignant Tumors (Goldstraw et al, 2007). If the lung cancer is diagnosed in its earliest stages, cure is possible through surgery or chemo-radiation therapy. Unfortunately, cases of lung cancer are most often detected relatively late in the illness, which makes cure less likely. However, with appropriate treatment, survival and prognosis can be improved considerably. For patients with locally advanced or metastatic NSCLC, 5-year survival rates are approximately 14% for Stage IIIA, 5% for Stage IIIB, and 1% for Stage IV (American Cancer Society).

Management of patients with advanced NSCLC is individualized on the basis of molecular and histologic features of the tumor, and is discussed in Section 1.2 (Chemotherapy), Section 1.2.2 (Targeted therapy) and Section 1.3 (Immunotherapy).

1.2. Treatment Options for Locally Advanced or Metastatic NSCLC

1.2.1. Chemotherapy for Locally Advanced or Metastatic NSCLC

1.2.1.1. First-line Treatment for Advanced NSCLC Without an EGFR Mutation or ALK Rearrangement

For previously untreated patients with advanced NSCLC who do not harbor epidermal growth factor receptor (EGFR) sensitizing mutation or anaplastic lymphoma kinase (ALK) gene translocation, platinum-containing doublet chemotherapy regimens are recommended

(NCCN, 2017). No advantage has been noted with addition of a third cytotoxic drug (Delbaldo et al, 2004). A meta-analysis of randomized trials comparing either cisplatin or carboplatin with a third-generation drug revealed that there was no apparent difference between a carboplatin-based or cisplatin-based chemotherapy when assessing overall survival (OS) or 1-year survival rates (American Cancer Society). However, some differences in adverse event (AE) profiles were noted, so the authors recommend factoring which therapy is more appropriate for a given patient into decisions (NCCN, 2017).

For patients with non-squamous NSCLC that does not have a sensitizing mutation in EGFR or an ALK fusion oncogene, standard first-line therapy includes a chemotherapy doublet of cisplatin and pemetrexed, which has been shown to have a superior efficacy and reduced toxicity compared to cisplatin and gemcitabine (NCCN, 2017; Alimta package insert; Al- Farsi and Ellis, 2014). The median (95% confidence interval [CI]) OS was 11.0 (10.1 to 12.5) months for pemetrexed plus cisplatin compared to 10.1 (9.3 to 10.9) months for gemcitabine plus cisplatin.

Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (Roviello et al, 2017). Though a combined analysis of the Eastern Cooperative Oncology Group (ECOG) 4599 and POINTBREAK trials found survival benefit with the addition of bevacizumab to carboplatin/paclitaxel in patients younger than 75 years (de Castria et al, 2013), the ECOG and National Comprehensive Cancer Network (NCCN) only recommend bevacizumab/chemotherapy for select patients with advanced non-squamous NSCLC because more significant toxicities were observed with bevacizumab/chemotherapy compared to chemotherapy alone (NCCN, 2017). Doublet chemotherapy regimens are recommended in the NCCN guideline and the Chinese guideline for patients with non-squamous NSCLC who are lacking the certain gene dysregulation; bevacizumab/chemotherapy is a treatment option for this population.

For patients with squamous NSCLC, cisplatin and gemcitabine or cisplatin and paclitaxel are broadly accepted as standard treatment regimen (NCCN, 2017; Al- Farsi and Ellis, 2014).

1.2.1.2. Second-line Treatment for Advanced NSCLC Without an EGFR Mutation or ALK Rearrangement

Patients clinically or radiologically progressing after first-line chemotherapy should be offered second-line therapy if their ECOG performance status (PS) is 0 to 2. In the second-line setting, combination chemotherapy regimens failed to show any OS benefit over single-agent treatments (Di Maio et al, 2009). Single agents improve disease-related symptoms and OS. There are currently 4 chemotherapeutic and targeted agents approved that are commonly used in the second-line setting: docetaxel, pemetrexed, erlotinib, and afatinib. The choice of agents depends upon a number of factors, including tumor histology, the patient's comorbidities, toxicity from previous treatments, risk of neutropenia, smoking history, and patient preference. Patients with a good PS in second-line trials have a median survival duration of approximately 8 to 9 months and may receive 2 salvage therapies during the course of their treatment (Stinchcombe and Socinski, 2008).

Docetaxel was the first agent to demonstrate a survival benefit in comparison with best supportive care (BSC) in patients with relapsed NSCLC following platinum-containing therapy. In the first randomized Phase 3 study (TAX317), 103 eligible patients were stratified by PS and

best response to cisplatin chemotherapy and were then randomized to treatment with docetaxel 100 mg/m^2 or 75 mg/m^2 (55 patients) or BSC. Time to progression was longer for docetaxel-treated patients than for BSC-treated patients (10.6 versus 6.7 weeks, respectively; P <.001), as was median OS (7.0 versus 4.6 months; log-rank test, P=.047). The difference was more significant for patients treated with docetaxel 75 mg/m^2 than with docetaxel 100 mg/m^2 and there was less toxicity with docetaxel 75 mg/m^2 than with docetaxel 100 mg/m^2 (Shepherd et al, 2000). Subsequent studies comparing other treatment options with docetaxel in a second-line setting showed a response rate of 6% to 11% and median OS of 5 to 10 months (Barnfield et al, 2016).

Pemetrexed appears to be a non-inferior agent compared with docetaxel. A Phase 3 study demonstrated non-inferiority for OS between pemetrexed and docetaxel (8.3 versus 7.9 months, hazard ratio [HR] 0.99, 95% CI: 0.8 to 1.2). However, pemetrexed showed a better toxicity profile with a significantly lower rate of neutropenia and alopecia as well as lower rates of gastrointestinal AEs (Hanna et al, 2004). However, use of pemetrexed is limited to patients with non-squamous histology. In addition, its use as a first-line agent has become much more prevalent, thus limiting its administration in the second-line setting.

Erlotinib was shown to improve survival as compared with BSC in a randomized study that included patients with poor PS (ECOG PS of 2 or 3) (Shepherd et al, 2005). Therefore, erlotinib is the preferred option for patients who cannot receive cytotoxic chemotherapy because of poor PS.

Afatinib was compared with erlotinib in a Phase III trial in squamous-type NSCLC and showed better efficacy in progression-free survival (PFS) and OS. Thus, afatinib could be an additional option for the treatment of patients with ECOG PS 0 to 2 and locally advanced or metastatic squamous cell carcinoma progressing on or after platinum-based chemotherapy (Soria et al, 2015).

1.2.2. Targeted Therapy for Locally Advanced or Metastatic Lung Cancers

Advances in understanding of the molecular pathogenesis of lung cancer have led to the identification of several specific targets for therapeutic agents. Targeting EGFR and ALK has played a central role in advancing NSCLC research, treatment, and patient outcome over the last several years. Several small molecular targeted agents have been approved globally for patients with NSCLC harboring certain gene dysregulation (Schettino et al, 2013).

Such small molecule tyrosine kinase inhibitors including drugs that inhibit EGFR (eg, erlotinib, gefitinib, icotinib, afatinib, osimertinib) and that target rearranged ALK (eg, crizotinib, certinib, alectinib) are especially effective in patients whose tumors harbor a sensitizing EGFR mutation or an ALK fusion gene. In Asian population, the EGFR mutation rate among adenocarcinoma is around 40%, and can be up to 65% such as in non-smoking Chinese female patients with adenocarcinoma of lung, which is significantly higher than that in the western countries, ~10 - 15% (Shi et al, 2014). And a small number (approximately 5%) of NSCLCs express the fusion form of ALK in China, which is similar to that reported in Caucasian population (Zhou and Zhou, 2015).

The ROS proto-oncogene 1 (ROS1) oncogene encodes an orphan receptor tyrosine kinase related to ALK (Shaw et al, 2014). Crizotinib was approved for metastatic NSCLC whose tumors are

ROS1-positive. Crizotinib monotherapy showed marked antitumor activity with the objective response rate (ORR) of 72% in patients with advanced ROS1 rearranged NSCLC in an expansion cohort of the Phase 1 study. However, no head-to-head clinical trial of crizotinib versus first-line doublet chemotherapy demonstrating superiority is available in this population. Doublet chemotherapy as first-line treatment is still an option for this population.

1.3. Anti-PD-1/PD-L1 Therapy for Locally Advanced or Metastatic Lung Cancers

Lung cancer has been historically considered poorly immunogenic, with no established benefit from cytokine modulation or vaccines. However, the recent development of checkpoint inhibitors provided a promising new approach for immunotherapy in patients with NSCLC.

Immune check point-inhibitory receptor, programmed cell death protein-1 (PD-1) is mainly expressed in activated T cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (Topalian et al, 2012; Bersanelli and Buti, 2017). It is presumed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor (TCR) and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. Expression by PD-1 is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of PD-1 ligand, programmed cell death protein ligand-1 (PD-L1), is significantly increased in tumor cells (TCs) and tumor-associated immune cells in the presence of stimulating cytokines, such as interferon-alpha and interferon-gamma in the tumor microenvironment. Furthermore, increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor and tumor-associated stromal cells have been observed in many types of solid tumors including NSCLC (Jin and Yoon, 2016; Patel and Kurzrock, 2015; Van Der Kraak et al, 2016; McDaniel et al, 2016; Gong et al, 2011). Based on these observations, monoclonal antibodies blocking the interaction between PD-1 and PD-L1 have been developed and have recently been shown to be promising anticancer immunotherapeutic agents in a variety of tumor types including NSCLC.

The PD-1 inhibitors, pembrolizumab and nivolumab, are both immunoglobulin G4 (IgG4) antibodies, which bind to PD-1 to disrupt the interaction between PD-1 and its ligands (PD-L1 and programmed cell death protein ligand -2 [PD-L2]) and thereby impede inhibitory signals in T cells (Wang et al, 2014; Garon et al, 2015). Nivolumab is Food and Drug Administration (FDA)-approved for treatment as a single agent or in combination with ipilimumab (Cytotoxic T Lymphocyte-Associated Antigen 4 [CTLA-4] antagonist) of unresectable or metastatic melanoma, metastatic NSCLC that progresses on or after platinum-based chemotherapy, and advanced renal cell carcinoma after anti-angiogenic therapy, classical Hodgkin's lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation and post-transplantation brentuximab vedotin, and head and neck squamous cell cancer with disease progression on or after a platinum-based therapy (Antonia et al, 2016b; United States FDA, 2017; Motzer et al, 2015; Gettinger et al, 2015; Weber et al, 2015; Hodi et al, 2016; Rizvi et al, 2015a, Hellmann et al, 2017).

The Phase III Checkmate-057 trial compared nivolumab with docetaxel in 582 pretreated patients with non-squamous type NSCLC. It showed a significant prolongation of OS in the nivolumab group (median OS 12.2 versus 9.4 months, HR=0.73, 95% CI: 0.59 to 0.89; P=0.002),

although a small excess of early progression and/or death events were observed for nivolumab compared with docetaxel. In addition, ORR (19% versus 12%, P = 0.021) and duration of response (DoR) (17.2 versus 5.6 months) were in favor of nivolumab, and no significant difference has been reported for PFS (median PFS 2.3 versus 4.2 months, HR=0.92, 95% CI: 0.77 to 1.1). An exploratory retrospective analysis revealed an association of efficacy by nivolumab and the level of tumor membrane expression of PD-L1. However, this analysis is limited by the retrospective and unplanned nature of this biomarker assessment (Borghaei et al, 2015). In the Phase III Checkmate 017 trial, nivolumab was compared with docetaxel in 272 pretreated patients with squamous cell lung cancer; significant prolongation of OS was shown in the nivolumab group compared with the docetaxel group (median OS was 9.2 versus 6.0 months) and the risk of death was 41% lower with nivolumab than with docetaxel (HR=0.59; 95% CI: 0.44 to 0.79; P<0.001). At 1 year, the OS rate was 42% (95% CI: 34 to 50) with nivolumab versus 24% (95% CI: 17 to 31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel (P = 0.008). The median PFS was 3.5 months with nivolumab versus 2.8 months with docetaxel (HR for death or disease progression, 0.62; 95% CI: 0.47 to 0.81; P<0.001). The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit (Brahmer et al, 2015).

Pembrolizumab is another anti-PD-1 monoclonal antibody (IgG4) that has received FDA approval for the treatment of any histological type of NSCLC after failure of first-line therapy in patients with tumors expressing PD-L1. In the Phase 3 KEYNOTE-010 trial, 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of TCs were randomized to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 once every 3 weeks. The primary end points were OS and PFS both in the total population and in the patients with PD-L1 expression on at least 50% of TCs. In the entire population, OS was significantly longer for pembrolizumab 2 mg/kg versus docetaxel (HR=0.71, 95% CI: 0.58 to 0.88; p=0.0008) and for pembrolizumab 10 mg/kg versus docetaxel (HR=0.61, 95% CI: 0.49 to 0.75; p <0.0001), with median OS of 10.4, 12.7 and 8.5 months in the 3 arms, respectively. Pembrolizumab achieved a better outcome for those patients with high PD-L1 expression (>50%) (Herbst et al, 2016).

Atezolizumab is a humanized anti-PD-L1 monoclonal antibody that interrupts PD-L1 binding to PD-1 and B7-1. Atezolizumab is FDA-approved for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy and for treatment of patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy (Tecentriq package insert). In the Phase III OAK study, 850 patients were randomized to receive atezolizumab or docetaxel. The OS was significantly longer with atezolizumab than with docetaxel in the intent-to-treat (ITT) and PD-L1 positive populations. In the ITT population, OS was improved with atezolizumab compared with docetaxel (median OS was 13.8 months [95% CI: 11.8 to 15.7] versus 9.6 months [8.6 to 11.2 months]; HR=0.73 [95% CI: 0.62 to 0.87], p=0.0003). The OS in the TC1/2/3 or IC1/2/3 population was improved with atezolizumab (n=241) compared with docetaxel (n=222; median OS was 15.7 months [95% CI: 12.6 to 18.0] with atezolizumab versus 10.3 months [8.8 to 12.0] with docetaxel; HR=0.74 [95% CI: 0.58 to 0.93], p=0.0102). Patients in the PD-L1 low or undetectable subgroup (TC0 and IC0) also had improved survival with atezolizumab (median OS was12.6 months versus 8.9 months; HR=0.73 [95% CI: 0.59 to 0.96]). The OS improvement was similar in patients with squamous (HR=0.73

[95% CI: 0.54 to 0.98]; n=112 in the atezolizumab group and n=110 in the docetaxel group) or non-squamous (0.73 [0.60 to 0.89]; n=313 and n=315) histology (Rittmeyer et al, 2017).

A summary of anti-PD-1/PD-L1 monoclonal antibody (mAb) clinical trial outcomes in the second- or third-line setting is presented in Table 1.

Table 1: Anti-PD-1/PD-L1 Monoclonal Antibody Clinical Trial Outcomes

Publication	Population Name	Primary Endpoint	Therapy	N	mOS (months)	HR		mPFS (months)	HR	
Brahmer New England Journal of Medicine 373: 123 (2015)	Squamous CHECKMATE-017	OS	Nivolumab	135	9.2	0.59		3.5	0.62	
			Docetaxel	137	6.0			2.8		
Borghaei New England Journal of Medicine 373: 1627 (2015)	Non-squamous CHECKMATE-057	OS	Nivolumab	292	12.2	0.73		2.3	0.92	
			Docetaxel	290	9.4			4.2		
Herbst Lancet 387: 1540 (2016)	PD-L1 ≥1% Squamous and non-squamous KEYNOTE-010	OS and PFS All and PD-L1 ≥50%	Pembrolizumab 2 mg/kg	345	10.4	0.71 (ITT) 0.54 (Dx)		3.9	0.88	
			Docetaxel	343	8.5		0.61 (ITT) 0.50 (Dx)	4.0		0.79
			Pembrolizumab 10 mg/kg	346	12.7			4.0		
Rittmeyer Lancet 389: 255 (2017)	Squamous and non-squamous OAK	OS All and TC1/2/3 or IC1/2/3	Atezolizumab	425	13.8	0.73 (ITT) 0.74 (1+2+3+) 0.67 (2+3+) 0.41 (3+)		2.8	0.95	
			Docetaxel	425	9.6			4.0		

Abbreviations: Dx = programmed cell death protein ligand-1 positive population; HR = hazard ratio; ITT = intent-to-treat (population); IC1/2/3 = programmed cell death protein ligand-1 membrane staining on immune cell; mOS = overall survival duration in months; mPFS = progression-free survival duration in months; OS = overall survival; PD-1 = programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; PFS, progression-free survival; TC1/2/3 = programmed cell death protein ligand-1 membrane staining on tumor cell.

Avelumab, is the second FDA-approved anti-PD-L1 antibody, with its first indication approved for advanced urothelial bladder cancer as second-line therapy (Apolo et al, 2017; United States FDA, 2017) and other registration trials ongoing including in NSCLC. Durvalumab is the third FDA-approved anti-PD-L1 antibody with its first indication for second-line treatment of advanced urothelial bladder cancer. In addition, positive interim analysis results were released for the PACIFIC trial of durvalumab as maintenance therapy of inoperable Stage III NSCLC after curative chemo-radiation therapy (Antonia et al, 2017).

In the first-line setting, pembrolizumab monotherapy was associated with significantly longer progression-free and OS and with fewer AEs than was platinum-based chemotherapy in chemo-naïve, PD-L1+ (>50% TCs), EGFR and ALK wild type NSCLC patients (Reck et al, 2016). The KEYNOTE-024 study randomly assigned 305 patients to receive either pembrolizumab or the investigator's choice of platinum-based chemotherapy. Median PFS was 10.3 months versus 6.0 months in the pembrolizumab and chemotherapy group (HR 0.50; 95% CI, 0.37 to 0.68; P<0.001). The estimated rate of OS at 6 months was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR 0.60; 95% CI, 0.41 to 0.89; P=0.005). The ORR was higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%), and treatment related AEs of any grade were less frequent, as were Grade 3, 4, or 5 treatment related AEs (26.6% vs. 53.3%). Based on these results, FDA-approved pembrolizumab in metastatic NSCLC for first-line treatment of patients whose tumors have high level of PD-L1 expression. In contrast, in Checkmate 026, it was reported that nivolumab failed to show any benefit compared with standard platinum-based chemotherapy in metastatic NSCLC patients with PD-L1 expression >1% TC. Study was stratified by PD-L1 expression (<5% vs ≥5% TC) and histology. Median PFS in the PD-L1 ≥5% NSCLC group was 4.2 months (nivolumab) versus 5.9 months (chemotherapy; HR, 1.15; 95% CI: 0.91 to 1.45, P=0.25). No benefit was observed in the PD-L1 ≥50% subgroup either (Socinski et al, 2016).

Also in the first-line setting, pembrolizumab was recently FDA-approved in combination with pemetrexed and carboplatin for the first-line treatment of metastatic non-squamous NSCLC, irrespective of PD-L1 expression (Keytruda package insert). This is based on the positive results of the Phase II study KEYNOTE-021 Cohort G1, in which 123 previously untreated patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations were randomized in the pembrolizumab plus pemetrexed/carboplatin or the chemotherapy only group. ORR was nearly double in the immune-chemo group than pemetrexed/carboplatin alone: 55% (95% CI = 42–68) compared to 29% (95% CI = 18–41), respectively; all responses were partial responses (PRs). Among patients who received pembrolizumab plus pemetrexed/carboplatin, 93% had a DoR of 6 months or more (range = 1.4+ to 13.0+ months) compared to 81% who received pemetrexed/carboplatin alone (range = 1.4+ to 15.2+ months). In addition, findings demonstrated an improvement in PFS (HR = 0.53; 95% CI = 0.31–0.91, P =.0205), with a median PFS of 13.0 months (95% CI = 8.3–not estimable) for patients treated with pembrolizumab plus pemetrexed/carboplatin compared to 8.9 months (95% CI = 4.4–10.3) with pemetrexed/carboplatin alone (Langer, 2016).

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

Tislelizumab is a humanized IgG4 variant monoclonal antibody against programmed cell death protein-1 (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 as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks the binding of both programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2), inhibiting PD-1 mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab consistently and dose-dependently enhanced the functional activity of human T cells and pre-activated, primary peripheral blood mononuclear cells. In addition, tislelizumab demonstrated antitumor activity in several allogeneic xenograft models in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer] and BCLU-054 [NSCLC]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to gamma fragment crystallizable region receptor IIIA (Fcγ RIIIA) and complement 1q, a subunit of complement 1, by in vitro assays, suggesting a low to no antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity effect in humans (Labrijn et al 2009). Unlike natural IgG4 antibody, tislelizumab has no observable fragment antigen-binding (Fab)-arm exchange activity by the in vitro assay, predicting the antibody would be stable in vivo and unlikely to form bispecific antibodies.

Tislelizumab binds to cynomolgus monkey and human PD-1 with similar affinity, but does not bind to mouse PD-1 due to the significant sequence divergence from human and monkey PD-1. Therefore, cynomolgus monkeys were considered to be the relevant species for nonclinical safety evaluation.

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

1.4.2. 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 cynomolgus monkeys. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice (GLP) regulations. The single dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole blood assay. The toxicokinetic profile was well characterized with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the

systemic exposure. The No Observed Adverse Effect Level (NOAEL) of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study.

Please refer to the tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.4.3. Clinical Pharmacology

In the Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim pharmacokinetic analysis (data cutoff date of 28 August 2017) was conducted using noncompartmental analysis methods, using serum concentrations from patients who received doses of tislelizumab 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks and patients who received doses of 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 (C_{max}) and the area under the plasma or serum concentration time curve [AUC]) increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg /kg, both after single-dose administration and 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 (CL) of tislelizumab was 0.173 L/day, volume of distribution (Vd) in the central and peripheral compartments of 2.89 L and 1.76 L respectively, and half-life ($T_{1/2}$) was approximately 19 days. Race, gender, and body weight were not significant covariates on the CL of tislelizumab, which supports fixed-dosing across different ethnic groups.

1.4.4. Summary of Relevant Clinical Experience with 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 Investigator's Brochure for more detailed information on efficacy and safety of tislelizumab.

1.4.4.1. 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 Population 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 (GGT) 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.
- 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 stable disease.
- Preliminary efficacy from the NSCLC cohort (with a data cutoff of 26 December 2017) include a response rate of 14.3% (6/42 patients, 4 confirmed PR +2 unconfirmed PR, all ongoing) with responses seen regardless of PD-L1 expression status, and stable disease in 23 patients (55%) and lasting for ≥6 months in 9 patients.

1.4.4.2. 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 Population 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 from the NSCLC cohort (08 December 2017 data cutoff) include an ORR of 10% (4/39 patients with confirmed PR, 2 each PD-L1 positive and negative), and stable disease in 20 patients (51%).

1.4.4.3. 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, one case of fatal myocarditis and polymyositis was reported in 1 patient who received a single dose of tislelizumab, in combination with paclitaxel and cisplatin.

Please refer to the tislelizumab Investigator's Brochure for more detailed information.

1.5. Study Rationales

1.5.1. Rationale for Tislelizumab in NSCLC as Second-or Third-Line Treatment

Despite recent improvements in treatments, the prognosis for patients with advanced NSCLC remains dismal, with median OS of approximately 12.5 months (Sandler, 2006). Patients who

receive second-line treatment for their disease have an even more limited prognosis, with median survival duration of only 8 months (Stinchcombe and Socinski, 2008). Currently approved therapies are associated with significant toxicities (eg, neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life.

Approved anti-PD-1/PD-L1 mAbs have shown superior efficacy to docetaxel by increasing the OS about 2 to 3 months in the second- or third-line setting in advanced NSCLC patients who have disease progression during or after a platinum-containing regimen. Tislelizumab is a novel anti-PD-1 mAb for which IgG gamma Fc Receptors (FcγRs) binding ability has been specifically engineered out. High levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, myeloid derived suppressor cells [MDSCs], etc.) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 mAb treatment, possibly via Fc-FcγR mediated antibody-dependent cellular cytotoxicity or antibody-dependent cellular phagocytosis depletion of effector T cells (Gül et al 2015; Prieto et al 2015; Makarova-Rusher et al 2015; Dahan et al 2015). Large numbers of immunosuppressive myeloid derives supperessor cells expressing high levels of FcγRs in NSCLC is known to dampen immune response by depleting antitumor effector cells with PD-1 expression (Antonia et al, 2016a). Given absent FcγR binding and thereby minimal antibody-dependent cellular cytotoxicity/antibody-dependent cellular phagocytosis effect, tislelizumab may show better efficacy and lower toxicity in NSCLC patients.

According to the latest preliminary data outlined in Section 1.4.4, tislelizumab monotherapy exhibits a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies (Section 1.6)

1.5.2. Rationale for Docetaxel as the Active Control for Second- and Third-Line Treatment

In the second- and third-line treatment setting for NSCLC, docetaxel remains a commonly used standard treatment option for both squamous and non-squamous histologies in China and worldwide. It has demonstrated a survival benefit relative to BSC in patients with relapsed NSCLC following first-line therapy and is associated with a response rate between 6% and 11% and a median OS of 5 to 10 months (see Section 1.2.1.2). In Checkmate-057/-017, Keynote-010 and OAK studies, the pivotal trials for nivolumab, pembrolizumab and atezolizumab registration in the United States and Europe, docetaxel was chosen as active control in the second-or third-line setting to anti-PD-1/PD-L1mAbs (Borghaei et al, 2015; Brahmer et al, 2015; Herbst et al, 2016; Rittmeyer et al, 2017). A median OS of 7 to 10 months was observed in the docetaxel arms across these studies, which is in the range with efficacy reports of docetaxel in a Phase 3 study comparing docetaxel with pemetrexed as second-line treatment in Chinese NSCLC patients (Sun et al, 2013). Based on the above mentioned studies, docetaxel has been chosen as the active control in the current study with an assumption of 10 months median OS. The use of docetaxel as the active control is consistent with other pivotal trials of anti-PD-1 mAb and will make this study more interpretable when comparing the results with the published data.

1.5.3. Rationale for Stratification Factors

After screening for eligibility and signing of informed consent, approximately 800 eligible patients will be randomized in a 2:1 ratio to receive tislelizumab or docetaxel. A stratified randomization will be implemented in which patients will be stratified by histology (squamous

versus non-squamous), line of therapy (2 versus 3) and PD-L1 expression level on tumor cell membrane (<25% versus ≥25%). Among the 3 proposed stratification factors, the first 2 are important prognostic factors in NSCLC. Histology has been a clinical feature driving therapeutic decision; while line of therapy is also included in NSCLC treatment guidelines for the consideration of therapy selection. Patients with one prior line of systemic therapy and/or non-squamous tumor generally have better prognosis (eg, longer PFS/OS) than patients in the other categories. PD-L1 expression as a predictive marker in immunotherapy has been investigated in previous second-line NSCLC trials. It has been reported that expression of PD-L1 on TCs correlates with response to anti-PD-1 or anti-PD-L1 therapy (Borghaei et al, 2015; Herbst et al, 2016; Rittmeyer et al, 2017). Based on these observations, PD-L1 was selected as a stratification factor in this study, and it is the Sponsor's hypothesis that patients with higher PD-L1 expression may achieve greater clinical benefit from tislelizumab. The PD-L1 expression status will be measured by immunohistochemistry assay in a central laboratory and using the Ventana PD-L1 (SP263) antibody. PD-L1 is defined as positive if ≥25% of TCs express PD-L1, and PD-L1 is defined as negative if <25% of TCs express PD-L1 (Rebelatto et al, 2015).

Therefore, the proposed stratified randomization will achieve better treatment assignment balance. It will help to increase the precision of the estimate of treatment effect and to make the results more interpretable.

1.5.4. Rationale for Randomization at 2:1 Ratio

Published data shows superior efficacy is achieved with anti-PD-1/PD-L1 mAb treatment as compared with docetaxel in advanced NSCLC patients who experienced disease progression during or after treatment with a platinum-containing regimen. A 2:1 ratio will not weaken the statistical power of the study because the numbers of deaths in the interim and final analyses are adjusted upwards by 13% from a 1:1 randomization so the power is at least 80% for the hypothesis testing in ITT Analysis Set and PD-L1 positive subset. Compared with a 1:1 ratio, eligible patients will have 17% higher chance to benefit from tislelizumab treatment based on the medical assumption made for this study which will make the trial more attractive. The Sponsor believes a 2:1 randomization is unlikely to compromise the safety of patients in the trial given the safety data observed in other tislelizumab trials so far and the safety monitoring plan proposed in the trial. The randomization ratio could provide more information from the tislelizumab treated patients with high PD-L1 expression, a subset of special interest.

1.5.5. Rationale for Choosing Overall Survival in ITT and PD-L1-positive Subset as Dual Primary Endpoint

Anti-PD-1/L1 mAbs monotherapy has been approved in second- and third-line NSCLC based on Phase 3 trials showing an OS benefit in the ITT population compared to docetaxel (Table 1). Subgroup analyses for different PD-L1 expression indicate a trend for longer OS and higher ORR in the higher PD-L1 expression group than the low/intermediate or negative groups, especially in non-squamous lung cancer pathological types (Table 1). As NSCLC tumors with low PD-L1 expression are less likely to respond to anti-PD-1/ PD-L1 mAb treatment and given that multiple ongoing first or second-line trials limit enrollment to only patients with high tumor PD-L1 expression (Antonia, 2017), this may lead to an over-representation of patients with PD-L1 low tumors in this study. To mitigate the risk of obtaining skewed PD-L1 distribution toward low expression due to competing trials enrolling only patients whose tumor PD-L1 expression is

high, adjustment to enrollment will be made by capping the PD-L1 negative and low population to ~60% of ITT. This will be accomplished through the Interactive Web Response Technology (IWRT) system, when necessary, such that the percentage of PD-L1 positive patients is no less than 40% of the ITT Analysis Set, based on the reported prevalence of PD-L1 positivity is ~40% in the NSCLC population (Rebelatto, 2015, Antonia, 2017). The OS will be tested in both the ITT Analysis Set and PD-L1 positive subsets while the overall type I error is controlled at 0.05 (two-sided). It should be noted that the patient enrollment criteria (ie, PD-L1 cutoff) are determined prior to the randomization (see Section 3.1); as well as other key design elements (ie, α spent in the PD-L1 positive subset, timing and number of deaths included in the final analysis of the PD-L1 positive subset (see Section 9.2.1 and Section 9.7), testing sequence of the secondary endpoints in the PD-L1 positive subset). Therefore, the statistical inference made with respect to the PD-L1 positive subset is held to the same standard as trials with a single primary hypothesis in terms of statistical rigor.

The Sponsor believes that a statistically significant result from the proposed OS test in the PD-L1 positive subset alone would provide convincing evidence of survival benefit of tislelizumab over docetaxel in this population, and thus it would support full approval of the indication in the second- and third-line therapy of NSCLC patients with high PD-L1 expression.

1.5.6. Rationale for Patient Population Excluding Patients with EGFR Mutation and ALK Translocation

Patients harboring EGFR sensitizing mutation or ALK translocation have better prognoses than those with wild type EGFR and ALK. EGFR and ALK inhibitors are standard care for patients harboring the respective genetic disorders. Second- or third-generation tyrosine kinase inhibitors are available for patients who developed resistance to first-line treatment. For those patients with acquired resistance to EGFR TKIs by mechanisms other than T790M mutation, clinical trials investigating compounds targeting alternative mechanisms such as cMet amplification are underway. The percentage of EGFR sensitizing mutations is higher in Chinese NSCLC patients as compared with Caucasian population, 40% versus 15%, respectively. In Chinese female patients with lung adenocarcinoma, the EGFR mutation rate is up to approximately 65% (Shi et al, 2014). A similar frequency for ALK gene transfusion is observed in Chinese NSCLC patients (~4 to 5 %) as in the Caucasian population (Li et al, 2013).

Published data suggest the efficacy of anti-PD-1 mAb therapy was not superior to docetaxel in patients with EGFR mutant tumors. Subset analysis in EGFR mutant patients, albeit small numbers, did not show benefit from checkpoint inhibitor monotherapy over docetaxel (Lee et al, 2017). It was confirmed that mutation burden as well as presence of mutations in DNA repair genes were correlated with anti-PD-1 response in NSCLC, which has been considered as another predictive biomarker for response of checkpoint inhibition (Rizvi et al, 2015b). It is known that EGFR mutation is associated with adenocarcinoma in patients with none or light smoking history (Shi et al, 2014). It is suspected that mutation load in these patients may be lower compared with EGFR wild type NSCLC patients, which underline the lower response rate and shorter OS to anti-PD-1 mAb treatment. In addition, low PD-L1 expression is correlated with the presence of EGFR mutations in Chinese patients (Ji et al, 2016). Due to the low likelihood for EGFR mutant NSCLC patients to benefit from anti-PD-1 mAb treatment, the present study will exclude this subpopulation of patients. There were not enough patients with

ALK translocation for subgroup analysis in the completed trials testing anti-PD-1/PD-L1 mAbs. However, these patients are managed well with targeted therapy at first-line or second-line setting, thus they will be excluded from this study.

1.5.7. Rationale for Tislelizumab Dose Selection

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.

Rates of treatment-related adverse events (AEs) and serious adverse events (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 overall 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 CL 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 BORs of progressive disease (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 .

1.6. Benefit-Risk Assessment

Available data from clinical trials of other anti-PD-1 antibodies, such as nivolumab, and pembrolizumab, have demonstrated favorable efficacy/safety profiles. Other immunotherapy targeting PD-1s/PD-L1s, such as atezolizumab and avelumab, showed manageable safety profiles and approved antitumor activity in patients with advanced lung cancer (refer to Section 1.3). The efficacy data with tislelizumab in NSCLC patients is preliminary but consistent with other anti-PD1/PD-L1 monoclonal antibodies.

According to the latest data collected from the Phase 1 trial of BGB-A317_Study_001, tislelizumab has demonstrated a favorable safety profile that is consistent with known class effects of other anti-PD-1 antibodies (refer to Section 1.3). Antitumor activity with tislelizumab monotherapy has been observed in a range of tumor types (refer to Section 1.4.4).

The present study is a randomized study designed to compare the safety and efficacy of A317 with docetaxel in patients with advanced non-squamous NSCLC with wild type EGFR or squamous NSCLC. The benefit/risk assessment based on available tislelizumab Phase 1 data and

the publication from Phase 3 trials of other anti-PD-1 antibodies is considered as positive; the trial design, which randomizes patients to tislelizumab and docetaxel at a 2:1 ratio, is considered as justified for risk management.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

- To compare the efficacy, as measured by OS, of tislelizumab with docetaxel in the second- or third-line setting in patients with NSCLC who have progressed on a prior platinum-containing regimen. A comparison of the treatment arms will be performed in:
  - The ITT Analysis Set
  - The PD-L1 positive Analysis Set, where PD-L1 positive is defined as ≥25% of TCs with PD-L1 membrane staining via the Ventana SP263 assay

2.1.2. Secondary Objectives

- To compare the efficacy of tislelizumab and docetaxel as measured by ORR, DoR, and PFS per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 in:
  - The ITT Analysis Set
  - The PD-L1 positive Analysis Set
- To compare health-related quality of life (HRQoL) between tislelizumab and docetaxel arms
- To evaluate the safety and tolerability of tislelizumab versus docetaxel

2.1.3. Exploratory Objectives

- To compare tumor assessment outcomes (ie, DCR, and clinical benefit rate [CBR]) between tislelizumab and docetaxel assessed by investigator per RECIST v1.1
- To explore potential predictive biomarkers for efficacy including but not limited to PD-L1 expression, tumor mutational burden (TMB), gene expression profile (GEP), and tumor-infiltrating immune cells
- To characterize the PK of tislelizumab in patients with NSCLC
- To determine host immunogenicity to tislelizumab in patients with NSCLC

2.2. Endpoints

2.2.1. Primary Endpoints

- OS - defined as the time from the date of randomization to the date of death due to any cause in the ITT and PD-L1 positive Analysis Set

2.2.2. Secondary Endpoints

- ORR – defined as the proportion of patients in the ITT and PD-L1 positive Analysis Set who had a CR or PR as assessed by the investigator per RECIST v1.1

- DoR – defined as the time from the first occurrence of a documented objective response to the time of relapse, as determined by the investigator per RECIST v1.1, or death from any cause, whichever comes first, in the ITT and PD-L1 positive Analysis Set
- PFS – defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by the investigator per RECIST v1.1 or death from any cause, whichever occurs first, in the ITT and PD-L1 positive Analysis Set
- HRQoL – measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ-LC13) and Core 30 (EORTC QLQ-C30), and European Quality of Life 5-Dimensions, 5-level (EQ-5D-5L) scale
- Incidence and severity of TEAEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), v4.03

2.2.3. Exploratory Endpoints

- DCR – defined as the proportion of patients whose best overall response (BOR) is CR, PR or stable disease (SD) per RECIST v1.1
- CBR - defined as the proportion of patients who have CR, PR and SD that is ≥24 weeks in duration per RECIST v1.1
- PD-L1 expression, TMB, GEP, and tumor-infiltrating immune cells as predictive biomarkers for response
- Summary of serum concentrations of tislelizumab in the PK Analysis Set
- Assessments of immunogenicity of tislelizumab by determining the incidence of ADAs in the ADA Analysis Set

3. STUDY DESIGN

3.1. Summary of Study Design

This is a randomized, open-label, multicenter Phase 3 study in adult patients with histologically confirmed, locally advanced or metastatic (Stage IIIB or IV), EGFR wild type NSCLC (squamous or non-squamous) who have disease progression during or after a platinum-containing regimen. Histology of NSCLC (squamous or non-squamous) will be confirmed at the investigator's site. Patients with known EGFR mutation or ALK rearrangement are ineligible for the study. For non-squamous NSCLC patients, documentation of wild type EGFR by tissue-based test is required to enter the study.

Patients must have been treated with at least 1 platinum-containing regimen but not more than 2 chemotherapy regimens and have disease progression during or following chemotherapy treatment. Patients who progressed or have disease recurrence during or after neo-adjuvant or adjuvant therapy with platinum-containing regimen (counted as one line of therapy) within 6 months are eligible to enroll into the study.

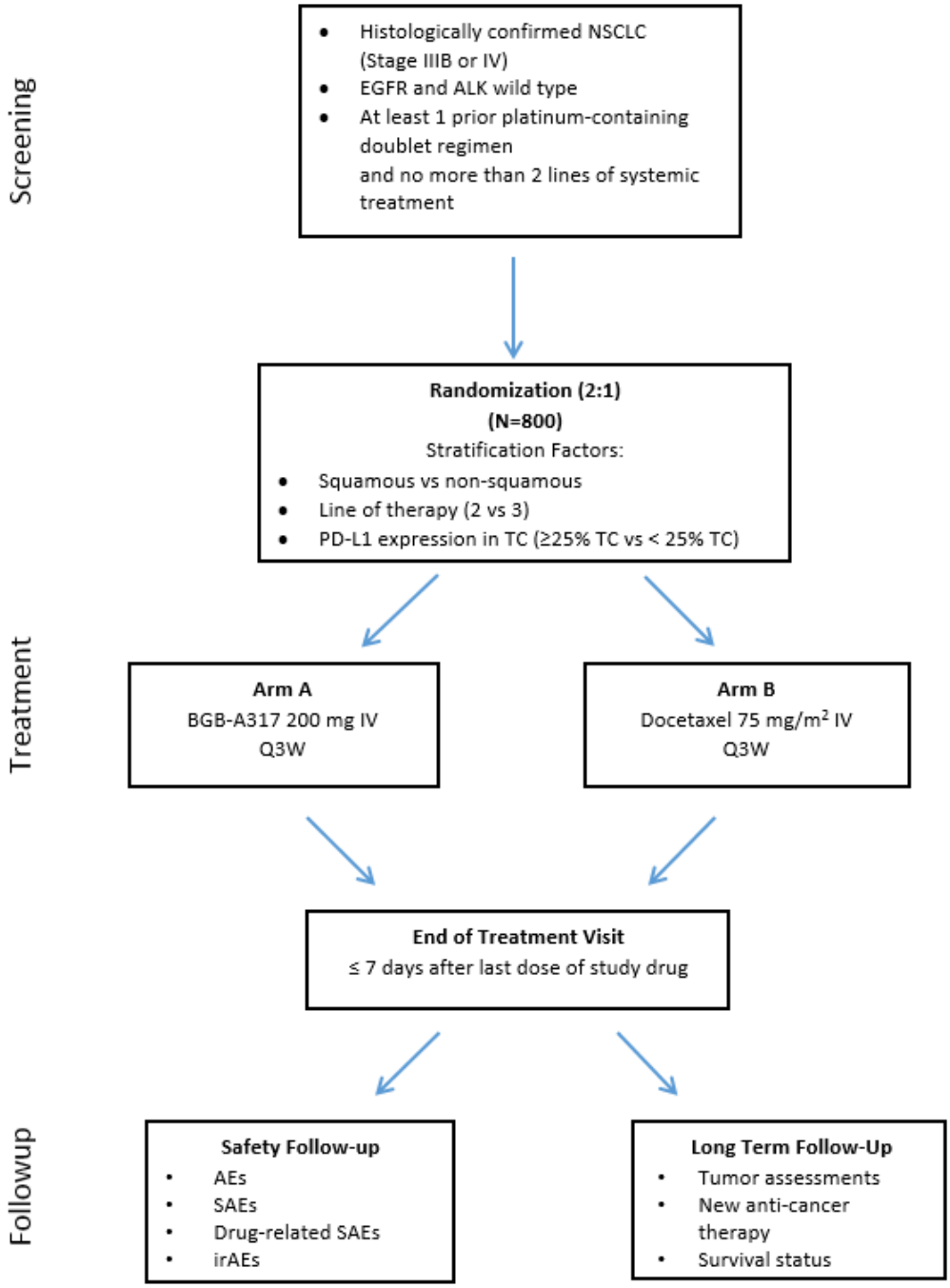
Tumor specimens from eligible patients will be prospectively tested for PD-L1 expression by a central laboratory (see Section 7.5). The study will enroll all eligible patients whose tissue is evaluable for expression testing, regardless of PD-L1 expression status. The PD-L1 expression status remains to be blinded to the Sponsor, patients and investigators and only open to Independent Data Monitoring Committee (IDMC). In the case that continued monitoring of patient enrollment would project the prevalence of PD-L1 negative or low patients on study to be higher than 60%, enrollment may be limited to PD-L1-selected patients whose tumors show expression of ≥25% on tumor cells (TCs) by SP263 immunohistochemistry for the remainder of the study to ensure adequate enrollment in PD-L1 positive and negative patients (see also Section 1.5.5 and Section 10.1).

The study procedures will occur over a Screening Phase (up to 28 days prior to randomization); Treatment Phase (until disease progression, intolerable toxicity, or withdrawal of informed consent, whichever occurs first); Safety Follow-up Phase (up to 30 days following last study treatment or initiation of new anticancer therapy, whichever occurs first for any AEs and up to 90 days following last dose of tislelizumab for irAEs, regardless of whether or not the patient starts a new anticancer therapy); and a Survival Follow-up Phase.

A schedule of efficacy and safety assessments is presented in Appendix 1.

The study schematic is provided in Figure 1.

Figure 1: Phase 3 Study Schema for Tislelizumab Versus Docetaxel as Second-or Third-Line Therapy for NSCLC



Abbreviations: AE = adverse event; ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; irAE = immune-related adverse event; IV = intravenously; NSCLC = non-small cell lung cancer; PD-L1 = programmed cell death protein ligand-1; Q3W = once every 3 weeks; SAE = serious adverse event; TC = tumor cells; vs = versus; WT = wild type; yr = year.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate will sign the informed consent form prior to undergoing any screening procedure (refer to Appendix 1 for details). Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the Screening Period to assist the determination of suitability on the study, as described in Section 7.1.4. Respective test results need to be submitted to the Sponsor. Tests may be repeated as clinically indicated while on study (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Patients with EGFR mutation or ALK rearrangement are ineligible for the study. Patients with wild type or unknown status of ALK are eligible to enroll. For patients with non-squamous NSCLC, documentation of wild type EGFR by tissue-based test is required to enter the study. For undocumented cases, fresh or archival tumor tissues are required for central EGFR mutation assessment. Archival tumor tissues (not restricted to pretreatment) will be collected for biomarker analysis at a central laboratory. If archived formalin-fixed paraffin-embedded (FFPE) tissue is not sufficient, a fresh biopsy sample will be needed. Refer to Section 7.8 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be randomized in a 2:1 ratio to receive either tislelizumab or docetaxel treatment. Randomization will be stratified by histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression (≥25% TC versus <25% TC).

Patients will receive open-label treatment with one of the following:

Arm A: Tislelizumab 200 mg IV once every 3 weeks until disease progression assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

Arm B: Docetaxel 75 mg/m^2 IV once every 3 weeks until disease progression assessed by the investigator per RECIST v1.1, unacceptable toxicity, or withdrawal of informed consent, whichever occurs first.

Patients receiving tislelizumab will be permitted to continue tislelizumab treatment beyond radio-imaging progression if clinical benefit is seen in the absence of symptomatic deterioration and unacceptable toxicity per investigator's discretion. Specific requirements for post-progression continuation of patients treated with tislelizumab are described in Section 7.5.

Radiological assessment of tumor response status will be evaluated by investigators every 9 weeks (± 7 days) for the first 12 months, then every 12 weeks (± 7 days) from Year 2 onwards. Response will be assessed by the investigator using RECIST v1.1. Details are provided in Appendix 2.

Safety will be assessed throughout the study by monitoring AEs/serious adverse events (SAEs) (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03, and laboratory abnormalities. Vital signs, physical

examinations, Eastern Cooperative Oncology Group (ECOG) performance status change, and electrocardiogram (ECG) results will also be used for safety assessment. Safety assessments are further detailed in Section 7 and the Schedule of Assessments (Appendix 1).

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

3.4. Safety Follow-Up

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (to occur within 30 days [± 7 days] after the last dose of either study drug, or before the initiation of a new anticancer treatment, whichever occurs first). In addition, telephone contacts with patients should be conducted to assess immune-related AEs and concomitant medications (if appropriate, ie, associated with an immune-related AE) at 60 days (±14 days), and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-related AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.7.

The End of Treatment visit at which a response assessment showed progressive disease, resulting 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 7.5.

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

3.5. Survival Follow-up

Patients who discontinue study drug for reasons other than disease progression (eg, toxicity) or death will continue to undergo tumor assessments according to Section 7.4.4 and the Schedule of Assessments (Appendix 1), until the patient experiences disease progression, withdraws consent, loss to follow-up, death or until the study completes, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information after discontinuation of the study treatment via phone contact (with either the patient or the patient's guardian, if applicable), review of patient medical records, and/or in-person clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit or as directed by the Sponsor until death, loss to follow-up, withdrawal of consent, or study completes by the Sponsor.

3.6. Discontinuation From the Study Treatment or From the Study

3.6.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue the study at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study at any time. Patients who

discontinue study treatment for reasons other than disease progression should be followed for assessments of antitumor activity (Section 7.5), safety, (Section 3.4) and survival (Section 3.5), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate eCRF.

Reasons a patient may be discontinued from the study may include, but are not limited to the following:

- Patient withdrawal of consent
- Pregnancy
- Any medical condition that the investigator determines may jeopardize the patient's safety, if he or she were to continue in the study
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and Chinese (or other Country) patent medicines] for the treatment of cancer)
- Patient noncompliance

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

Patients may discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Patients have completed all study assessments

3.7. End of Study

Study termination is defined as the time point when data collection will stop. The primary analyses will be conducted when the predefined death events have been observed (see Sections 9.2 and 9.3) for the efficacy and safety evaluations. The study will continue until the last patient has died, becomes lost to follow-up, or withdraws from study, or until Sponsor decides to terminate the study.

The Sponsor has the right to terminate this study at any time. Reasons for 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.
- Overall patient enrollment is unsatisfactory.

The Sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit and Safety Follow-up Visit.

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

The Sponsor has the right to close a site at any time. The decision will be communicated to the site in advance. 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
- Noncompliance with Good Clinical Practice, applicable laws and regulations
- Study activity is completed (ie, all patients have completed and all obligations have been fulfilled)

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study.

1. Able to provide written informed consent and can understand and comply with the requirements of the study and the schedule of assessments.
2. Age ≥ 18 years on the day of signing the informed consent form (or the legal age of consent in the jurisdiction in which the study is taking place).
3. Histologically confirmed disease which is currently locally advanced or metastatic NSCLC of either squamous or non-squamous histology.
4. With disease progression during or following treatment with at least one platinum-containing regimen.
    - Patients who received prior neo-adjuvant or adjuvant chemotherapy but progressed within 6 months after last dose are eligible provided the target lesion(s) have not been previously treated with local therapy (radiation) or the target lesion(s) within the field of local therapy have subsequently progressed as defined per RECIST v1.1
    - Note: No more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease
        – Chemotherapy regimens will be counted on the basis of interval disease progression and not the number of agents or switches in agents (eg, a first-line therapy that consists of several cycles of a platinum doublet and subsequent maintenance therapy that introduces or switches to a new chemotherapy agent without interval disease progression will all be considered one chemotherapy regimen).
        – Adjuvant/neo-adjuvant chemotherapy or chemo-radiation counts as a prior chemotherapy regimen if ≤ 6 months have elapsed between the last dose and the date of recurrence. Combined treatment with chemotherapy and radiation constitutes a single regimen; surgery is not considered a regimen.
    - Anti-EGFR treatment with disease progression as the treatment outcome is counted as a line of therapy.
    - Anticancer agents used for pleurodesis are not counted as a line of therapy.
5. Patients must be able to provide archival/fresh tumor tissues (FFPE blocks or approximately 11 [at least 5] freshly cut unstained FFPE slides) for biomarker analysis to assess PD-L1 expression and, provided sufficient tissue, including tumor mutational burden (TMB), and gene expression profiling (GEP). Documentation of wild type status of EGFR by tissue-based test must be provided for patients with non-squamous NSCLC prior to enrollment. For undocumented cases, archival/fresh tumor tissues (FFPE blocks or 6 freshly cut unstained FFPE slides) are required for central assessment of EGFR

mutation. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 42 days before Cycle 1 Day 1) is mandatory (written informed consent is required prior to fresh tumor biopsies).

6. ECOG PS ≤ 1 (Table 5).
7. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 28 days prior to randomization):
   - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, and hemoglobin ≥ 90 g/L. Note: Patients must not have required a blood transfusion or growth factor support within the 14 days before sample collection
   - Estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 6)
   - Total serum bilirubin ≤ 1.5 × upper limit of normal (ULN)
     - ≤ 3 × ULN, if Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of the elevation
   - Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 × ULN
     - ≤ 5 × ULN, if liver metastases
8. Females of childbearing potential must be willing to practice highly effective method of birth control (Appendix 4) for the duration of the study, and, for patients in Arm A, for at least 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test within 7 days of randomization.
9. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and, for patients in Arm A, for at least 120 days after the last dose of tislelizumab.
10. Expected life span > 12 weeks.

4.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons.

1. Received prior docetaxel treatment for metastatic disease or prior immune checkpoint inhibitor therapies targeting PD-1, PD-L1 or CTLA-4.
2. Diagnosed with NSCLC that harbors EGFR sensitizing or driver mutation or ALK gene translocation.
   - Patients with a known EGFR mutation are ineligible. Patients with non-squamous histology and unknown EGFR mutational status will be required to be tested prior to enrollment. Testing can either be performed locally and results submitted for eligibility review or submitted for central laboratory evaluation during the Screening Period; if EGFR mutation status is found to be positive, the patient will be ineligible for the study. For patients with squamous histology, given that testing for EGFR mutation is not considered standard in this patient population due to its low

frequency, patients with an unknown status will not be required to be tested at screening (Chiu, et al, 2014).

- Patients with a known ALK fusion oncogene are excluded. Patients (non-squamous or squamous histology) with unknown ALK fusion oncogene status will not be required to be tested at screening given that testing for ALK fusion is not considered standard in squamous type patient population and a low frequency in non-squamous type.
- If local testing results for EGFR mutation is not available for patients with non-squamous histology, an additional 6 unstained tumor specimen sections may be required for central evaluation of these biomarkers.

3. Patients with toxicities (as a result of prior anticancer therapy including radiation) which have not recovered to baseline or stabilized, except for AEs not constituting a likely safety risk (including but not limited to alopecia, rash, pigmentation, specific laboratory abnormalities etc).
4. Received chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin), or investigational agent, used to control cancer ≤ 28 days (or ≤ 5 half-lives, whichever is shorter) prior to randomization
5. Received any herbal medicine used to control cancer within 14 days prior to randomization.
6. History of severe hypersensitivity reactions to other mAbs.
7. History of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
8. Patients with significantly impaired pulmonary function, or who require supplemental oxygen at baseline.
   - An assessment of pulmonary function is to be conducted at screening (see Section 7.1.4)
9. Clinically significant pericardial effusion.
10. Clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to randomization.
11. Active Leptomeningeal disease or uncontrolled, untreated brain metastasis:
    - Patients with a history of treated and, at the time of screening, asymptomatic CNS metastases are eligible, provided they meet all the following:
      – Brain imaging at screening shows no evidence of interim progression
      – Have measurable disease outside the CNS, only supratentorial metastases allowed
      – No ongoing requirement for corticosteroids as therapy for CNS disease; anticonvulsants at a stable dose allowed
      – No stereotactic radiation or whole brain radiation within 14 days prior to randomization

- Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases.
  - Following treatment, these patients may then be eligible, provided all other criteria, including those for patients with a history of brain metastases, are met.

12. Major surgical procedure requiring general anesthesia, or significant traumatic injury ≤ 28 days prior to randomization, or anticipation of need for major surgical procedure during the course of the study.
    - Placement of vascular access device is not considered major surgery.
13. Malignancy other than NSCLC.
    - Any active malignancy ≤ 2 years before randomization except for the specific cancer under investigation in this study with the exception of those with a negligible risk of metastasis or death, such as localized and adequately treated malignancies (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).
14. Severe chronic or active infections (including tuberculosis infection) requiring systemic antibacterial, antifungal, antiviral therapy, or systemic oral/IV antibiotics within 14 days prior to randomization.
    - Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
15. A known history of human immunodeficiency virus (HIV) infection.
16. Patients with active/symptomatic carrier or chronic hepatitis B virus (HBV) whose HBV DNA ≥ 500 IU/mL (or ≥ 2500 copies/mL) should be excluded.
    - Note: Patients with detectable hepatitis B surface antigen (HBsAg) or HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at screening should have been treated for > 2 weeks prior to randomization and should continue treatment for 6 months after study drug treatment discontinues.
    - Note: Patients with active hepatitis C may enroll and those with detectable HCV RNA who are receiving antiviral therapy at time of screening should remain on continuous, effective antiviral therapy during the study
17. Active autoimmune diseases or history of autoimmune diseases that may relapse should be excluded. Patients with the following autoimmune diseases are allowed: controlled Type 1 diabetes, hypothyroidism managed with hormone replacement therapy only, controlled celiac disease, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), or diseases not expected to recur in the absence of external triggering factors (see Appendix 3).
18. Requiring systemic treatment with either corticosteroids (>10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of randomization.

a. A brief course (≤ 7 days) 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.
b. Adrenal replacement steroid dose ≤ 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
c. Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) are permitted.

19. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥ Grade 3 hypoalbuminemia ≤ 14 days before randomization.

20. Any of the following cardiovascular criteria:

a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization.
b. Symptomatic pulmonary embolism ≤ 28 days before randomization.
c. Acute myocardial infarction ≤ 6 months prior to randomization.
d. Heart failure of New York Heart Association Classification III or IV (see Appendix 5) ≤ 6 months prior to randomization.
e. Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to randomization.
f. Cerebral vascular accident or transient ischemic attack ≤ 6 months prior to randomization.
g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before randomization.
h. Any episode of syncope or seizure ≤ 28 days before randomization.

21. Prior allogeneic stem cell transplantation or organ transplantation.

22. Was administered a live vaccine ≤ 4 weeks before randomization.

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines, and are not allowed ≤ 4 weeks before randomization.

23. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs or result in insufficient or impaired compliance with study conduct.

24. Concurrent participation in another therapeutic clinical study.

5. STUDY TREATMENT

5.1. Packaging, Handling, and Storage

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, United States Pharmacopeia [USP] type I) containing a total of 100 mg antibody in 10 mL of isotonic solution. Tislelizumab was aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. One vial is packaged in a single carton box.

The label will include at a minimum, drug name, dose strength, contents, Sponsor, protocol number, kit number, batch/lot number, directions for use, storage conditions, caution statements, retest or expiry date, and space to enter the patient number and name of investigator. The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label. Tislelizumab must be stored at temperatures between 2°C and 8°C and protected from light.

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

5.1.2. Docetaxel

Docetaxel will be provided in vials for infusion. The contents of the label will be in accordance with all applicable local regulatory requirements.

Docetaxel must be kept at the temperature condition as specified on the label.

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

5.2. Dosage, Administration, and Compliance

The first dose of study drug is to be administered within 2 business days of randomization. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay, reduction, interruption or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5.

Table 2: Selection and Timing of Dose for Each Patient

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
Tislelizumab	200 mg	Every 3 weeks	Intravenous	See Section 3.3
Docetaxel	75 mg/m^2	Every 3 weeks	Intravenous	See Section 3.3

5.2.1. Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks).

Tislelizumab will be administered by IV infusion, using a volumetric pump (recommended to control infusion speed, but not required if infusion speed is controlled through alternative means consistent with approved institutional procedures) through an intravenous line containing a sterile, non-pyrogenic, 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.

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 afterwards in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes. If this is well tolerated then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Appendix 7 and Section 8.8.1.

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

5.2.2. Docetaxel

Docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or withdrawal of consent. Additional premedications should be administered as per standard practice. Please refer to the current docetaxel label for additional information.

5.3. Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted on the study drug administration electronic case report form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug will be recorded on the AEs eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.7. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products required for completion of this study (tislelizumab and docetaxel) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of investigational medicinal products. Any damaged shipments will be replaced.

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

Compliance will be assessed by the investigator and/or study personnel at each patient visit.

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

5.5. Dose Delay or Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.5.1. Dose Delay or Modification for Tislelizumab

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

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

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

Dose modification related to irAEs and infusion-related reactions are described in Appendix 7 and Section 8.8.1 respectively .

5.5.2. Dose Delay or Modifications of Docetaxel

Guidelines for docetaxel dose modifications to manage general toxicities are shown in Table 3.

Table 3: Guidelines for Docetaxel Dose Modifications

Adverse Event (Worst Grade in Previous Cycle)	Action to Be Taken
Febrile neutropenia/Grade 4 AGC ≥7 days	Withhold docetaxel until symptoms resolve.[a] Reduce docetaxel to 75% of previous dose (eg, from 75 mg/m^2 to 55 mg/m^2).
Grade 3 skin/neuropathy/major organ/non-hematologic toxicity	Withhold docetaxel until symptoms resolve. Reduce docetaxel to 75% of previous dose.
Grade 4 skin/neuropathy/major organ/non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction	Discontinue docetaxel treatment.

[a] Do not re-treat until AGC ≥1.5 × 10^9, platelets ≥100 × 10^9, and toxicity ≤Grade 2.
Abbreviations: AGC = absolute granulocyte count.

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils <500 cells/mm^3 (Grade 4) for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. Patients who develop Grade >3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Guidelines for the management of hepatotoxicity for docetaxel-treated patients are shown in Table 4.

Table 4: Guidelines for Management of Hepatotoxicity in Patients Receiving Docetaxel

	AST/ALT		Alkaline Phosphatase		Total Bilirubin	Docetaxel Dose
Mild to moderate	>1.5 × ULN	and	>2.5 × ULN		NA	75%
Severe	>3.5 × ULN*	and	>6 × ULN	OR	>1.5 x ULN**	Do not treat. Discontinue treatment if it is already started.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; ULN = upper limit of normal.*>5 x ULN if liver metastasis exists; **>3 x ULN if Gilbert Syndrome or indirect bilirubin approved to be extrahepatic

5.6. Disposal and Destruction

After completion of the study, all unused tislelizumab and docetaxel will be inventoried by the hospital unit pharmacist or other designated study center personnel. The inventoried supplies can be destroyed on site or at the depot according to institutional policies, after receiving written Sponsor approval.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients will not have received prior docetaxel treatment or therapies targeting PD-1, PD-L1, or CTLA-4.

6.2. Concomitant Therapy

6.2.1. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for the supportive care (eg, anti-emetics, anti-diarrheal) and in a patient's interest are allowed.

Systemic corticosteroids required for the control of irAEs must be tapered gradually (see Appendix 7) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The use of steroids > 10 mg/day as premedications of docetaxel for toxicity prophylaxis is permitted. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is also permitted.

Patients may continue to receive hormone replacement therapy or supportive care if initiated prior to enrollment. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to enrollment and at a stable dose. Patients receiving bisphosphonates during the trial for a non-malignant indication are permitted for this study.

Hematopoietic growth factors (ie, G-CSF or GM-CSF) are allowed according to institutional or other specific guidelines (eg, country, regional, or oncology organizations, such as American Society of Clinical Oncology [ASCO], etc.), while growth factors used as primary prophylaxis are not permitted. Growth factors must be discontinued for more than 48 hours prior to the next cycle of study drugs. The use of any growth factor support must be documented in the patient's record and eCRF.

Erythropoiesis stimulating agents are allowed for the treatment of cancer-related anemia in patients undergoing palliative treatment, in cases where hemoglobin is < 11 g/dL or a decrease of ≥ 2 g/dL from baseline, but only after the patient has been counseled about the risks and benefits of erythropoiesis stimulating agent use.

Patients with active hepatitis B defined as either detectable HBsAg or HBV DNA at baseline must initiate treatment 2 weeks prior to randomization or first dose, and continue until 6 months after the last dose. Patients should continue effective antiviral treatment during the study to decrease potential viral re-activation risk. Tenofovir and entecavir are recommended in the American Association for the Study of Liver Disease (AASLD) guideline because they lack resistance with long-term use (Terrault et al 2016; AASLD/IDSA HCV Guidance Panel, 2015). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator; however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.

BeiGene does not require patients with active hepatitis C to receive treatment with antiviral therapy. Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline or the local guidelines as appropriate. However, interferon-based therapy for either HBV or HCV is not permitted on study. Patients who are given antiviral therapy must initiate treatment at least 2 weeks prior to randomization or first dose.

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 provided 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 for RECIST v1.1.
  - The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation therapy or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigators' discretion after consultation with the sponsor medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

6.2.2. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine and Chinese patent medicines] for the treatment of cancer).
- Live vaccines within 28 days prior to randomization, while on study, and 60 days following the last dose of tislelizumab.
- Herbal remedies with immunostimulating 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.

For patients who receive docetaxel, any medications that have significant interactions with docetaxel (eg, substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4) should be avoided. Refer to the manufacturer's prescribing information for complete information regarding drug-drug interactions.

6.2.3. 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 or equivalent), except to treat or control a drug related AE (per protocol) or for short-term use as prophylactic treatment.
- Radiation therapy is not allowed, except for palliative or focally ablative radiation therapy, as described in Section 6.2.1.
- Systemic antibiotics are allowed to treat infection; however, tislelizumab should be held until the infection is resolved for at least one week before redosing with tislelizumab.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Patients should be instructed to avoid alcohol completely and should avoid other addictive drugs during the study.
- For use of live vaccines, refer to Section 6.2.2. For use of antivirals with HBV or HCV, refer to Section 6.2.1.

Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

7. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record and eCRF for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1. Screening

Screening evaluations will be performed within 28 days prior to randomization or enrollment (in non-randomized studies). Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure.

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests, unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.8) sections. The PK sampling schedule is shown in Appendix 1.

Rescreening under limited conditions may be allowed after consultation with BeiGene, eg, when a patient narrowly misses a laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.1.1. Demographic Data and Medical History

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status (ie, of childbearing potential or no childbearing potential), history of alcohol consumption and tobacco (ie, former or current or never), and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before randomization or the first dose. If appropriate, clinically significant disease should be graded according to NCI-CTCAE v 4.03 and reported in the Medical History eCRF.

Demographic data will include age and date of birth (in accordance with local country requirements), gender, and self-reported race/ethnicity.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 4 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

7.1.3. Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed by medical monitor to confirm that patients meet all eligibility criteria before randomization or first dose of study drug. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.4. Pulmonary Function Tests

Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the Screening Period to assist the determination of suitability on the study. Respective test results need to be submitted to the Sponsor.

For test results indicative of significantly impaired pulmonary function, eg, resting pulse oximetry <90% on room air and further de-saturation upon exercise, FEV1 <60% or DLCO (if performed) <60% of age and sex adjusted predicted performance levels (Pellegrino et al, 2005), the medical monitor needs to be consulted to confirm eligibility.

Tests may be repeated as clinically indicated while on study (refer to Appendix 1 for details).

7.2. Enrollment

7.2.1. Confirmation of Eligibility

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

After a patient is screened and the investigator determines the patient is eligible for randomization, study site personnel will complete an Eligibility Authorization Packet and send it to the medical monitor or designee to approve the enrollment. Study site personnel should ensure that a medical monitor's confirmation has been received before randomization.

7.2.2. Patient Numbering

After obtaining informed consent, study site personnel will access the IWRT system to assign a unique patient number to a potential study participant.

7.2.3. Enrollment/Randomization

After confirming the patient's eligibility, site personnel will access the IWRT system to randomize the patients and to assign study drugs. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.3. Tislelizumab and Docetaxel Dispensation

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

7.4. Safety Assessments

7.4.1. Vital Signs

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

For the first infusion of study drugs, the patient's vital signs should be determined within 60 minutes before the infusion, and during and 30 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before 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. Refer to Section 5.2.1 regarding precautionary monitoring of patients post infusion of tislelizumab.

7.4.2. Physical Examinations

A complete physical examination including an evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems should be performed at screening. Any abnormality identified at baseline will be graded according to NCI-CTCAE v 4.03 and should be recorded on the Medical History eCRF. Height (baseline only) and weight should be measured and recorded in the eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF. Refer to Section 8.4 for AE definitions, reporting, and follow-up.

7.4.3. Eastern Cooperative Oncology Group Performance Status

The ECOG PS (Table 5) will be assessed at the Screening Visit, pretreatment on Day 1 of each treatment cycle, End of Treatment Visit, and Safety Follow-up Visit.

Table 5: Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Laboratory assessments of serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified below.

If hematology and serum chemistry laboratory tests at screening are not performed within 7 days prior to administration of study drug(s) on Cycle 1 Day 1, these tests should be repeated and reviewed before study drug administration. Hematology and serum chemistry (including liver function tests) as specified below should be performed weekly for the first 3 cycles and at the beginning of subsequent cycles. After Cycle 1, results are to be reviewed within 48 hours before study drug administration.

Laboratory assessments will include the following:

- Hematology (complete blood count, including red blood cell count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, and basophils], and platelet count)
- Serum chemistry (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, direct bilirubin, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, albumin).
  - All patients will have creatine kinase (CK), creatine kinase-cardiac muscle isoenzyme (CK-MB)[1] testing at Screening and to be repeated at predose assessments in all treatment cycles, other scheduled visits during the first 3 treatment cycles, and at the end of treatment and safety follow-up visits.
    [1] In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.
- Coagulation tests (prothrombin time, partial thromboplastin time or activated partial thromboplastin time, international normalized ratio)
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation) and documented as negative within 7 days prior to Cycle 1 Day 1 (see Appendix 4)
- Urinalysis (complete [including, but not limited to specific gravity, pH, glucose, protein, ketones] and/or microscopic at screening and if clinically indicated)

- Thyroid function testing (thyroid stimulating hormone [TSH], free T3, free T4)
- HBV serology (antibodies against HBsAg, antibodies against hepatitis B core antigen [anti−HBcAb])
  - Patients who are HBsAg positive at screening must not be enrolled until the HBV DNA titres has been confirmed to be less than 500 IU/mL (see Section 4.2)
- Hepatitis C virus (HCV) serology (anti-HCV)
  - Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA

Details about sample collection and shipment will be provided in a separate instruction manual. Laboratory values obtained prior to screening will be performed at a local laboratory. For sites in China, on study clinical safety laboratory evaluations will be performed at a local laboratory; on study PK and biomarker evaluations will be performed at a central laboratory. For all other regions, baseline and on-study clinical laboratory evaluations (safety, PK, and biomarker testing) will be performed by a central laboratory. For all other regions, if Investigators believe that it is clinically indicated to obtain safety laboratory results from their own local laboratories on the day of the patient's visit, and before the results are returned from the designated central laboratory, they may do so at their discretion. Investigators may use results from local laboratories for assessing eligibility, safety monitoring and dosing decision. However, per protocol samples for the central laboratory must still be collected, since these serve as the official laboratory results for this study. Please refer to guidance document on use of central and local laboratories for study assessments.

7.4.5. Electrocardiogram

A 12-lead ECG is required at screening, Safety Follow-up, and as clinically indicated. When coinciding with blood draws at the same timepoint, ECG assessment should be performed prior to blood draws. ECG recordings should be performed after the patient has been resting in a semi-recumbent 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.

7.4.6. Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, v4.03 (NCI-CTCAE, June 2010). Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.4.

7.4.7. Ophthalmologic Examination

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) will be assessed by an appropriate specialist at screening. Either diagnostic

test captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used for the screening evaluation. Patients will undergo repeat assessments, preferably by utilizing the same test, by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days after the last dose of study treatment.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 7).

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to randomization. Results of standard of care tests or examinations (see Appendix 1) performed prior to obtaining informed consent and ≤28 days prior to randomization may be used for the purposes of screening rather than repeating the standard of care tests, provided they meet the screening requirements. During the study, tumor imaging will be performed approximately every 9 weeks (±7 days) during Year 1 and every 12 weeks (±7 days) from Year 2 onwards based on RECIST v1.1. Investigators may perform additional scans or more frequent assessments if clinically indicated.

Tumor assessments must include computed tomography (CT) scans (with oral/IV contrast, unless contraindicated) or magnetic resonance imaging (MRI), with preference for CT, of the chest, abdomen, and pelvis. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. For subsequent tumor assessments, the same radiographic procedure used to assess disease sites at screening are required to be used throughout the study (eg, the same contrast protocol for CT scans).

- An MRI (or CT scan if MRI is contraindicated or not readily available) scan of the brain is required for all patients during screening, ie, within 28 days of randomization, but ideally within 14 days of randomization, to confirm or refute the diagnosis of CNS metastases at baseline. Patients with brain metastases, including definitively treated stable CNS metastases may be eligible for the study (see Section 4.2).
- If a patient is known to have a contraindication to CT contrast media, a contrast enhanced MRI (preferred) or non-contrast CT should be performed.
- 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-positron emission tomography (NaF-PET) must be performed at screening. If bone scans have been performed within 3 months of randomization, the repeated scan is not required. 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 a CR is identified in target lesion 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, only if there is evidence of metastatic disease in

these regions at screening. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 2). 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. Tumor assessment will need to follow the original schedule after the confirmation scan.

For immune therapies such as tislelizumab, pseudoprogression may occur due to immune cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with tislelizumab until progressive disease is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease). If at the investigator's discretion a patient could continue to benefit from study treatment after progressive disease per RECIST v1.1 criteria, the patient may continue study treatment. The following criteria must be met in order to treat patients with suspected pseudoprogression or who may continue to benefit from study treatment after progressive disease:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records.

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

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

7.6. Pharmacokinetic Blood Sampling

Pharmacokinetic samples will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform PK sampling and handling. For tislelizumab, predose (within 60 min before start infusion) samples should be collected at Day 1 of Cycle 1, 2, 5, 9 and 17; postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1 and Cycle 5. An additional PK sample should be collected at the mandatory

Safety Follow-up Visit. If a patient presents with any ≥ Grade 3 irAE, additional blood PK samples may be taken to determine the serum concentration of tislelizumab.

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

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

7.7. Anti-Drug Antibody Testing

Tislelizumab may elicit an immune response. Patients with signs of any potential immune response to tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study (see Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

Serum samples will be tested for the presence of ADAs to tislelizumab using a validated immunoassay.

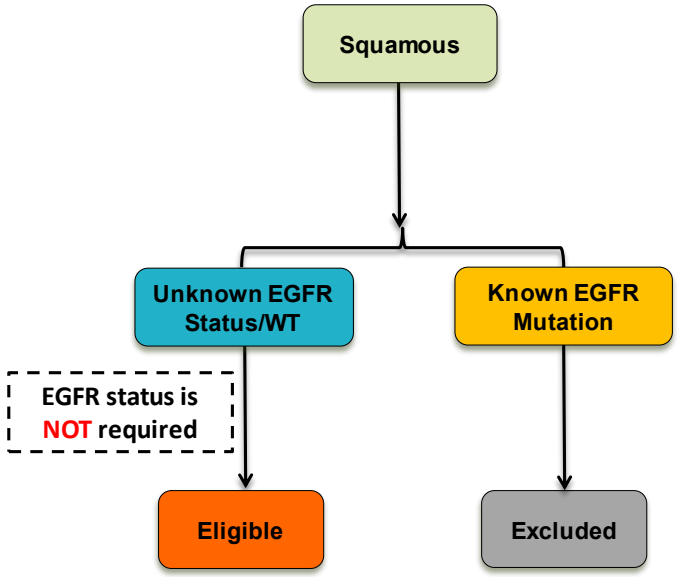
7.8. Tumor Tissues Samples and Biomarkers Assessment Procedures

Shipping, storage, and handling of archival tumor, fresh tumor, and leftover tumor tissue for the assessment biomarkers will be managed through a central laboratory. Refer to the Laboratory Manual for details of sample handling.

Archival tumor tissues (formalin-fixed paraffin-embedded block with tumor tissue or approximately 11 [a minimum of 5] unstained slides) are required to be sent to central laboratory for central immunohistochemistry assay of PD-L1 status. In addition to PD-L1 expression, other exploratory predictive biomarkers, including but not limited to TMB, GEP, and tumor-infiltrating immune cells, that are related to response or clinical benefit of tislelizumab may also be evaluated.

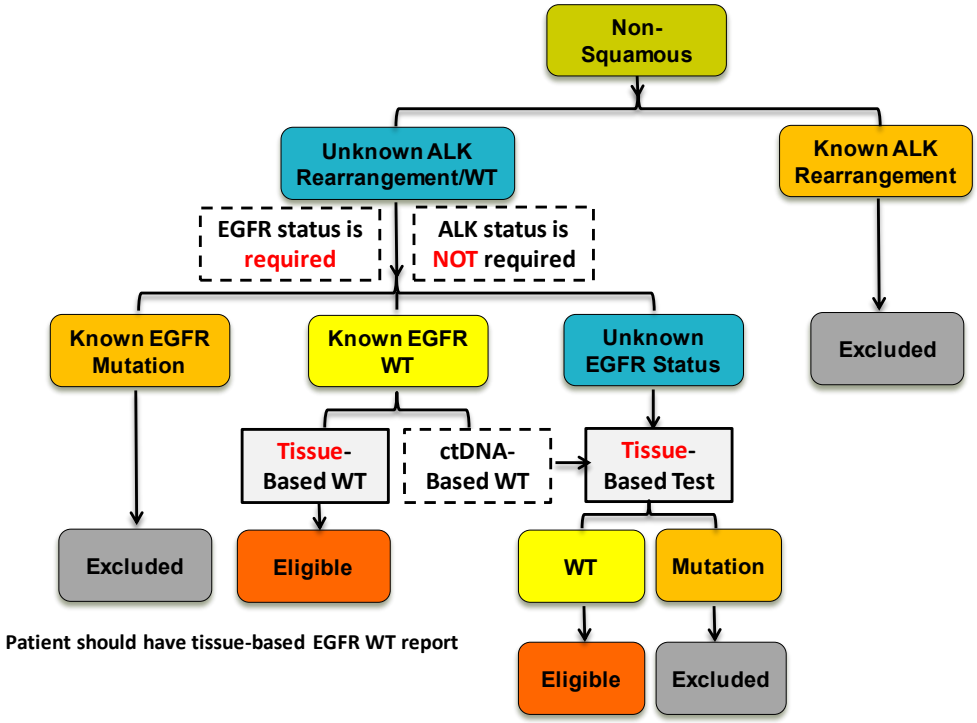
Screening tests for patients with squamous NSCLC are summarized in Figure 2. Screening tests for patients with non-squamous NSCLC are summarized in Figure 3. For patients with non-squamous NSCLC, documentation of wild type EGFR by tissue-based test is required before the patient enters the study. For undocumented cases, fresh or archival tumor tissues (FFPE block with tumor tissue or 6 additional freshly cut unstained FFPE slides) is required for the assessment of EGFR mutation at a designated central laboratory (slides should not be older than 90 days at time of sample submission). If archival tissues are insufficient for biomarker analysis, a fresh biopsy of a tumor lesion at baseline (within 42 days before Cycle 1 Day 1) is mandatory (written informed consent is required prior to fresh tumor biopsies). Refer to Section 4.1 for the inclusion criteria for details.

Figure 2: Screening tests for Squamous Cell NSCLC



Abbreviations: EGFR = epidermal growth factor receptor; WT = wild type

Figure 3: Screening tests for Non-Squamous Cell NSCLC



Abbreviations: ALK = anaplastic lymphoma kinase; ctDNA = circulating tumor DNA, EGFR = epidermal growth factor receptor; WT = wild type

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

If no or insufficient archival samples are available, a fresh tumor biopsy at baseline is required. 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.

7.9. Health-Related Quality of Life Assessment

Patients will be asked to complete the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer-13 Questions (EORTC QLQ-LC 13), and EQ-5D-5L before any clinical activities are performed, during on study clinic visits according to the schedule in Appendix 1. The questionnaires EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L will be completed in this sequence by the patients at the investigational site. The questionnaires will be provided in the patient's preferred language.

7.10. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted. Laboratory results should be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (refer to the visit window in Appendix 1), with subsequent dosing continued on the 21-day intervals accordingly, with a minimum of 14 days between tislelizumab dosing.

7.11. Unscheduled Visits

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated with Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. Limited safety data are available in human patients and the full safety profile has not been characterized. The following information is based on results from nonclinical and clinical studies and published data on 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 tislelizumab treatment and which are potentially immune-mediated are presented in Section 8.8.3.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures for suspected irAEs are provided in Appendix 7.

8.2. Risks Associated with Docetaxel

Please refer to the Table 6 for the reported toxicity for docetaxel. Because of the ethanol content in the docetaxel formulation, some patients may experience intoxication during and after treatment that should be monitored (and infusion rate decreased if appropriate). The investigator should refer to the package insert for a complete list of potential side effects.

Table 6: A Summary of the Commonly Reported Toxicities of Docetaxel

Most Common Side Effects	Less Common Side Effects (but May Be Severe or Life Threatening
• Myelosuppression ± infection or bleeding (may be severe) • Hypersensitivity (may be severe) • Fluid retention (may be severe) • Neuropathy (may be severe) • Cutaneous effects (including nails, may be severe) • Alopecia • Gastrointestinal (anorexia, nausea, vomiting, stomatitis, diarrhea, constipation) • Asthenia (may be severe)	• Secondary malignancy/leukemia • Cardiotoxicity, arrhythmia • Pneumonitis • Gastrointestinal obstruction, perforation, hemorrhage • Venous thromboembolism • Arterial thromboembolism • Disseminated intravascular coagulation • Seizures • Hepatotoxicity

8.3. General Plan to Manage Safety Concerns

8.3.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this trial. Results from the nonclinical toxicology studies 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, with a prior autoimmune disease that may relapse, patients who have undergone allogenic stem cell or organ transplantation, patients with evidence of severe chronic or active infections requiring treatment within 14 days, or hospitalization within 4 weeks prior to randomization, and patients who have received a live viral vaccine within 4 weeks before randomization are excluded from the study (see Section 4.2).

8.3.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all 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. Clinical laboratory results must be reviewed by investigator or appropriate delegate prior to the start of each cycle.

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

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomized to the tislelizumab arm, if treatment assignment is known. Administration of tislelizumab will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2.1).

All AEs will be recorded during the study (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of either study drug or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered 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 AEs.

Immune-related AEs will be recorded up to 90 days after the last dose of tislelizumab, 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.

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

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

8.4. Adverse Events

8.4.1. Definition and Reporting

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

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE).

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor. In this instance, all patient identifiers will be redacted on the copies of the medical records prior to submission to the Sponsor.

8.4.2. Assessment of Severity

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

Toxicities that are not specified in the NCI-CTCAE v4.03 will be defined as follows:

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

NOTE: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life threatening [Grade 4]), whereas seriousness is classified by the criteria based on the

regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities as described in Section 8.7.2.3.

8.4.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in the determination of his/her assessment.

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

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

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered "related" to study drug if any of the following are met:
- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.4.4. Following Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

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

New or updated information should be reported to the Sponsor according to the SAE instructions provided by the Sponsor within the time frames outlined in Section 8.7.2.1.

8.4.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, cardiac measures, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs . This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

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

8.5. Definition of a Serious Adverse Event

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

- Results in death.
- Is life threatening.

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

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

- Results in disability/incapacity.

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

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

The following are NOT considered SAEs:

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

8.6. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (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 serious adverse drug reaction (SADR), the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

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

8.7.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of either study drug or initiation of new anticancer therapy, whichever occurs first. In the tislelizumab arm, all irAEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs should be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

8.7.2. Reporting Serious Adverse Events

8.7.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 7.

Table 7: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

8.7.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the Sponsor within 24 hours as outlined in Section 8.7.2. The SAE report will always be completed as thoroughly as possible with all available details of the SAE, e-signed by the investigator, and forwarded to the Sponsor or designee within the designated time frames.

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

The investigator will always provide an assessment of causality for each SAE as described in Section 8.4.3.

The Sponsor will provide contact information for SAE receipt.

8.7.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 8.7.2.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

All SUSARs (as defined in Section 8.6) will be submitted to all applicable regulatory authorities and investigators for tislelizumab.

When a study center receives an initial or follow-up report or other safety information (eg, revised Investigator's Brochure) 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.

8.7.3. Eliciting Adverse Events

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

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

8.7.4. Disease Progression

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

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

8.7.5. Deaths

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

8.7.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or 30 days after the last dose of docetaxel, 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 adverse event, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

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

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

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

To determine the reporting requirements for individual SAEs, the Sponsor will assess the expectedness of the SAEs using the following Reference Safety Information documents:

- Tislelizumab Investigator's Brochure
- Local reference prescribing information for docetaxel (ie, EU SmPC, US label, China label, or other regional labels)

8.7.8. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 8.8.3) should be classified as irAEs and identified as such in the eCRF AE page until day 90, after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 7.

An extensive list of potential irAEs appears in Section 8.8.3, Table 9. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 7.

8.8. Management of AE 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 of infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE v4.03 criteria are outlined below.

8.8.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 8.

Table 8: 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 have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

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

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

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

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

8.8.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar et al, 2008). Patients should be instructed to report any delayed reactions to the investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the patient discontinued from the study.

The patients will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed and then the patient should be placed on monitor immediately and an Intensive Care Unit should be alerted for possible transfer if needed.

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

8.8.3. Immune-Related Adverse Events

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

A list of potential irAEs is shown below in Table 9. 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 and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018) and common immune-related toxicities are detailed in Appendix 7. For any AEs not included in Appendix 7 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 9: 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-barré syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Recommendations for management for irAEs are detailed in Appendix 7.

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

8.8.4. Renal Function Abnormalities

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

- If the serum creatinine is normal at baseline, please see Section 8.8.3 and refer to Appendix 7 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 7 for diagnosis and management of patients with abnormal renal laboratory values. Check the estimated GFR using Appendix 6 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the eGFR falls below 20 mL/min.

- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 7 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with the Sponsor medical monitor.

9. STATISTICAL METHODS AND ANALYSIS PLAN

The statistical analyses will be performed by the Sponsor or designee after the data collection for the primary efficacy and safety analyses are completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per Sponsor agreed reporting standards, where applicable.

The trial was originally designed to enroll patients from China and Asia Pacific (CAP) region. After amendment 1, it has been expanded to enroll patients from the rest of the world (ROW) as well. The primary and secondary objectives of the trial have not been changed due to this expansion. As of amendment 3.0, the number of death events that triggers interim analysis has been changed to 426 (approximately 76% of total number of 560 deaths) in the ITT Analysis Set. All analyses and testing discussed in Section 9 pertaining to study Analysis Set include both CAP and ROW patients. Statistical strategy in the ROW is discussed in Section 9.9. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Statistical Analysis

9.1.1. Randomization Methods

As discussed in Section 7.2.3, patients will be randomized using the IWRT system for this study by permuted block stratified randomization.

9.1.2. Analysis Sets

- The ITT Analysis Set includes all randomized patients. Patients will be analyzed according to their randomized treatment arms. This will be the primary Analysis Set for efficacy analysis. The ITT Analysis Sets will be summarized for both the China and Asia Pacific (ITT-CAP) Analysis Set and the rest of world (ITT-ROW) Analysis Set.
- The PD-L1 positive Analysis Set includes all randomized patients whose tumors were PD-L1 positive. Patients will be analyzed according to their randomized treatment arms. This will be the dual primary analysis population for efficacy analysis.
- Safety Analysis Set includes all patients who received at least one dose of study drug. It will be the population for the safety analyses.
- The PK Analysis Set includes patients who contributed at least one quantifiable postdose PK sample.
- The ADA Analysis Set includes all patients who have received at least 1 dose of tislelizumab for whom non-missing baseline ADA and at least 1 non-missing postbaseline ADA results are available.

9.1.3. Patient Disposition

The number of patients randomized, treated, discontinued from study drug and/or study and those with major protocol deviations will be counted. The primary reason for study drug and/or study discontinuation 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.

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics of the ITT Analysis Set will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include histology; prior line of therapy; PD-L1 expression in TC (≥25% TC versus <25% TC); gender; ECOG PS; race; smoking status; prior systemic therapies; and metastatic site. Demographic and disease characteristics will be summarized similarly in the PD-L1 positive Analysis Set.

9.1.5. Prior and Concomitant Medication

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 (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report for this protocol. Prior medications will be defined as medications that 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 (as of Safety Follow-up Visit). In addition, telephone contacts with patients should be conducted to assess irAEs and associated concomitant medications at 60 and 90 days (± 14 days) after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analysis

The overall type I error will be strongly controlled at a one-sided α of 0.025 within the 2 dual primary hypotheses and 4 secondary efficacy hypotheses. Initially, α of 0.02 and 0.007 will be assigned to the primary hypothesis testing in the ITT and PD-L1 positive Analysis Sets, respectively. The α allocation accounts for the positive correlation between the test statistics in the 2 Analysis Sets (ie, PD-L1 positive is a subset of the ITT Analysis Set). The overall type I error is controlled at 0.025 when at least 30% of the deaths in the ITT Analysis Set are from the PD-L1 positive subset. The α of 0.007 in the PD-L1 testing will be adjusted downwards if the final observed percentage is lower. When the trial proceeds to the final analysis, the OS hypothesis in the ITT Analysis Set will be tested first.

If the hypothesis in the ITT Analysis Set is rejected, the unused α will be passed on to the OS hypothesis test in PD-L1 positive Analysis Set; followed by the second efficacy hypothesis testing in the sequential order of ORR in the PD-L1 positive Analysis Set, DoR in the PD-L1 positive Analysis Set, PFS in the PD-L1 positive Analysis Set, PFS in the ITT Analysis Set, ORR in the ITT Analysis Set, DoR in the ITT Analysis Set, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/QoL in the ITT and PD-L1 Analysis Sets. Otherwise, if the OS hypothesis in the ITT Analysis Set cannot be rejected, hypothesis

testing will be carried out sequentially only in the PD-L1 positive Analysis Set for OS, ORR, DoR, PFS, lung cancer symptom scale measured by QLQ-LC13 and QLQ-C30 global health status/QoL scale at α of 0.007. The testing will continue until the first non-significant outcome occurs, following the methodology of Glimm et al (2010).

9.2.1. Primary Efficacy Analysis

9.2.1.1. Overall Survival

Overall Survival in the ITT Analysis Set:

OS will be compared between tislelizumab (Arm A) and docetaxel (Arm B) in a stratified log-rank test using a significance level of 0.02 (one-sided).

The null hypothesis to be tested is:

H_0: OS in Arm A = OS in Arm B

against the alternative hypothesis:

H_a: OS in Arm A ≠ OS in Arm B

This will be the primary analysis once the targeted numbers of deaths are reached in ITT Analysis Set.

The p-value from stratified log-rank test will be presented using stratification factors (see Section 1.5.3).

The median OS and the cumulative probability of OS at every 6 months if estimable, will be calculated for each treatment arm and presented with two-sided 95% CIs. Kaplan-Meier survival probabilities for each arm will be plotted over time.

The hazard ratio between tislelizumab and docetaxel ($HR_{A/B}$) and its 95% CI will be estimated using a Cox proportional hazard model with treatment arm as a factor and stratified by the actual value of the stratification factors.

Overall Survival in the PD-L1 Positive Analysis Set:

The hypothesis testing of OS in the PD-L1 positive Analysis Set will be carried out at a significance level of 0.007. If the OS hypothesis in the ITT Analysis Set is rejected, its corresponding α will be shifted to the testing in the PD-L1 positive Analysis Set (ie, a total α of 0.025). Similar statistical methods as described above will be applied with histology and line of therapy as strata in the stratified analyses.

Timing and Stopping Boundary in the Interim and Final Analyses of OS:

There will be one interim analysis of OS performed in the ITT Analysis Set. The interim analysis will be performed when approximately 426 deaths (76% of the target number of 560 deaths) among the 2 treatment arms are observed in the ITT Analysis Set. It is estimated that it will take approximately 23.1 months to observe 426 events. The final analysis of OS will take place after 560 deaths are observed in the ITT Analysis Set and 207 deaths are observed in its subgroup of patients with PD-L1 positive tumors. Thus, the predefined number of deaths in the ITT Analysis Set will trigger the interim and final analyses. The information fraction used in α spending function will be based on the observed number of deaths in the ITT Analysis Set at the

corresponding time points. A Hwang-Shih-DeCani spending function with γ parameter of -2 will be used in setting up the upper (efficacy) boundary. Stopping boundaries (p-value and Z score) of superiority test for OS at the interim and final analyses in the ITT Analysis Set, as well as OS at the final analysis in the PD-L1 positive Analysis Set are shown in Table 10. The boundaries for hypothesis testing in OS will be updated according to the actual numbers of death events in the interim and final analyses, using the pre-specified α spending function.

Table 10: Stopping Boundaries (p-value and Z score) and Approximate HR Threshold of Interim and Final Analyses of OS

	Time (months)	# Deaths	p-value (Z score) for Efficacy	Approximate HR Threshold for Efficacy
Interim analysis in ITT	23.1	426	<0.0112 (>2.28)	<0.791
Final analysis in ITT	31.0	560	<0.0153 (>2.16)	<0.824
Final analysis in PD-L1 positive	31.0	207	<0.007 (>2.46)	<0.696

Abbreviations: HR = hazard ratio; ITT = intent-to-treat (Analysis Set); PD-L1 – programmed cell death protein ligand 1

Subgroup Analyses

To determine if the treatment effect is consistent across various subgroups, the HR estimates of OS and its 95% CI will be estimated and plotted within each category of the following variables: PD-L1 expression in TC (≥25% TC versus <25% TC) in the ITT Analysis Set, histology (squamous versus non-squamous), line of therapy (2 versus 3), age (≤65 versus >65 years), gender (Female versus Male), ECOG PS (0 versus 1), smoking status and region (CAP versus ROW).

9.2.2. Secondary Efficacy Analysis

9.2.2.1. Objective Response Rate

The statistical significance of the difference in ORR between arms in the ITT Analysis Set will be evaluated using the Cochran-Mantel-Haenszel chi-square test with the actual stratification factors as strata. The two-sided 95% CIs for the odds ratio and the difference in ORR will be calculated, as well as Clopper-Pearson 95% CIs for the ORR within each arm.

9.2.2.2. Progression-Free Survival and Duration of Response

Progression-free survival will be compared between 2 arms in the ITT Analysis Set using a stratified log-rank test using actual stratification factors as strata.

The median PFS and the cumulative probability of PFS at every 3 months will be calculated for each treatment arm and presented with two-sided 95% CIs. PFS will be estimated using the Kaplan-Meier method. The PFS censoring rule will follow the (FDA Guidance for Industry 2007).

The actual tumor assessment visit date will be used to calculate PFS. Data for patients without disease progression or death at the time of analysis will be censored at the time of the last valid tumor assessment. Data for patients who start to receive new anticancer therapy or are lost to

follow-up will be censored at the last valid tumor assessment date prior to the introduction of new therapy or lost to follow-up. Patients who have a clinical determination of progression should undergo a CT/MRI, if possible, to correlate radiographic findings with the clinical findings. If a clinical determination of progression for a patient is confirmed, the date of the CT/MRI scan will be considered as the progression date for that patient. More details are provided in the Stastistical Analysis Plan.

The DoR will be analyzed similarly as the PFS. It will be summarized within responders. Efficacy outcomes (ie, ORR, DoR, and PFS) in the PD-L1 positive Analysis Set will be summarized similarly.

9.2.2.3. Health-Related Quality of Life

European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-LC13 and EORTC QLQ-C30) and EQ-5D-5L postbaseline scores will be compared between the 2 treatment arms, using a mixed model with baseline score and time since the randomization as covariates. Significant interaction between treatment and time since randomization or quadratic term of time since randomization (p-value<0.05) will also be included in the final model.

In addition, changes from baseline in global health status/QoL of QLQ-C30 and the functional and symptom scales of QLQ-C30, QLQ-LC13 and EQ-5D-5L (descriptive scores and visual analog scales) will be summarized descriptively.

9.2.3. Exploratory Efficacy Analysis

Exploratory efficacy endpoints assessed by investigator per RECIST v1.1, including DCR, and CBR, will be analyzed in the exploratory analysis.

The BOR will be defined as the best response recorded from start of study drug until data cut or start of new anticancer treatment. Patients with no post baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories (CR, PR, SD, and PD) will be presented by treatment arm.

The DCR and CBR will be analyzed similarly as the ORR in the ITT and PD-L1 positive Analysis Sets.

Analysis of the relationship of response to exploratory biomarker expression (eg, PD-L1 expression) may be carried out.

9.3. Safety Analysis

Safety will be assessed by monitoring and recording of 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.

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (in mg/3 weeks for tislelizumab and mg/m^2/3 weeks for docetaxel), and relative dose intensity.

The number (percentage) of patients requiring dose reduction for docetaxel, interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be classified into standardized medical terminology using MedDRA®. All AEs will be coded to MedDRA® (Version 18.1 or higher) by 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 (pretreatment) on or after the first dose of either study drug up to 30 days following study drug discontinuation or initiation of new anticancer therapy, whichever occurs first. TEAE classification also applies to irAEs and drug-related SAEs 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 PT. A patient will be counted only once by the highest severity grade per NCI-CTCAE v.4.03 within an SOC and PT, even if the patient experienced more than one TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug.

Treatment related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship (See Section 8.4.3). Serious adverse events; deaths; TEAEs of Grade 3 or above; irAEs; treatment related TEAEs; and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3. Clinical Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the Clinical Study Report for this trial. 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 in NCI-CTCAE v.4.03 will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs Analyses

Descriptive statistics for vital sign parameters and changes from baseline will be presented. Vital signs will be listed by patient and visit.

9.3.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.4. Pharmacokinetic Analyses

PK samples will be collected in this study as outlined in Appendix 1. PK samples will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual.

Tislelizumab serum concentration data, including but not limited to minimum observed plasma concentration (C_{trough}), will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

Additional PK such as population PK analyses may be conducted as appropriate.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results of these additional analyses may be reported separately from the Clinical Study Report.

9.5. Immunogenicity Analyses

Samples to assess anti-tislelizumab-antibodies will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform sampling, handling and processing procedures outlined in the Laboratory Manual.

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

9.6. Other Exploratory Analyses

Distribution of PD-L1 expression will be examined in the ITT Analysis Set. Association between PD-L1 expression (not restricted to the pre-specified cut off level of 25%) and tislelizumab treatment effect over docetaxel (OS, ORR, PFS, DoR, DCR, CBR) will be explored. Other potential predictive markers including but not limited to GEP, TMB, and tumor-infiltrating immune cells will be assessed.

Methodology for exploratory analyses is described in the Statistical Analysis Plan.

9.7. Sample Size Considerations

The original sample size calculation (ie, approximately 640 patients in China and Asia Pacific region) is based on the number of events required to demonstrate the OS superiority of Arm A to Arm B in ITT-CAP and ITT-CAP patients with PD-L1 positive tumors. The sample size has been increased to include an additional 160 patients from ROW, hence a total of approximately 800 patients will be recruited into the trial.

Six hundred and forty patients in ITT-CAP will be enrolled over a 16-month period at a constant enrollment rate and randomized in a 2:1 ratio to Arms A and B. The enrollment of 160 patients in ITT-ROW is expected to start approximately 8 months after that for the ITT-CAP and to last about 12 months. The median OS is assumed as 10 months in Arm B.

An interim analysis is planned when approximately 426 deaths in the ITT Analysis Set have been observed, which represents 76% of the planned number of events (ie 560) in the ITT Analysis Set for the final analysis. There is an approximately 87% power to detect an OS HR (Arm A/Arm B) of 0.75 with a one-sided type I error of 0.02 in the ITT.

A Hwang-Shih-DeCani spending function with γ parameter of -2 based on the information fraction in the ITT Analysis Set is used in setting up the upper (efficacy) boundary. The stopping boundaries in Table 10 will be updated based on the actual death events observed in the ITT Analysis Set at the interim and final analyses.

The superiority test of OS in the PD-L1 positive Analysis Set will be performed only in the final analysis. Two hundred and seven deaths in the ITT patients with PD-L1 positive tumors are required to have approximately 86% power to detect an OS HR of 0.60 with a one-sided type I error of 0.007. Assuming the prevalence of PD-L1 positivity is 40% in the ITT Analysis Set, it will take approximately 31.0 months to accumulate the required approximately 207 events in approximately 320 patients with PD-L1 positive tumors in the ITT Analysis Set.

As described in Section 1.5.5, the PD-L1 expression status will be closely monitored and enrollment of patients whose tumors are PD-L1 negative will be stopped as necessary through IWRT upon reaching ~60%, that is to ensure that the percentage of PD-L1 positive patients is no less than 40% of the ITT Analysis Set. The capping of PD-L1 negative patients to ~60% will be implemented in both ITT-CAP and ITT-ROW independently.

9.8. Interim Analyses

An interim analysis for OS in the ITT Analysis Set will be performed by an independent statistician external to BeiGene. The timing and stopping boundary of the interim analysis are described in Section 9.2.1. The IDMC is advised to make the recommendation of stopping the trial early for efficacy only when the early stopping boundaries for efficacy are crossed in the ITT Analysis Set. More details will be given in the IDMC Charter. The independent statistician will generate statistical outputs as described in the IDMC Charter and perform any ad-hoc analyses requested by the IDMC.

9.9. Statistical Strategy for ITT-ROW

Approximately 160 patients will be randomized in in the ITT-ROW in countries outside of China and Asia Pacific region, which consists of 20% of the ITT Analysis Set. With the additional region, the treatment effect of tislelizumab could be evaluated in a broader population, as well as its consistency between Asian and Caucasian populations. Subgroup analysis in the ITT-ROW is planned for descriptive purpose only due to the small sample size.

Selected efficacy and safety variables will be summarized in the ITT-ROW as subgroup analysis using similar methodologies discussed earlier.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Data Monitoring Committee

Regular safety monitoring (at least every 6 months) and efficacy monitoring will be performed by an IDMC. The IDMC may recommend modifications to the study including termination of the study due to safety and/or efficacy concerns. In addition, the IDMC will monitor on study prevalence of PD-L1 negative subset, and send an alert to the Sponsor when the PD-L1 negative subset is close to reaching 60% of the planned ITT Analysis Set sample size. The function and membership of the IDMC will be described in the IDMC Charter.

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

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

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include, but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

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

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

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

Site visits will be conducted by the Sponsor or an authorized representative 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.

12.4. Drug Accountability

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

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene's requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study, following drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, following drug inventory reconciliation by the monitor. These including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements specified in the Pharmacy Manual for disposal, arrangements will be

made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICAL CONSIDERATIONS

13.1. Ethical Standard

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

13.2. Institutional Review Board/Independent Ethics Committee

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

The principal investigator (or Sponsor) is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators (or Sponsor) are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 13.2.1). 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/EC. 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/EC and archived in the site's study file.

13.2.1. Protocol Amendments

All protocol amendments will be prepared by the Sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB or IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB or IEC and required site approval must be obtained by the Sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in Sponsor medical monitor or contact information).

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

13.3. Informed Consent

The Sponsor's sample informed consent form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/EC-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/EC-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/EC 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.

13.4. Patient and Data Confidentiality

The Sponsor maintains confidentiality and privacy 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 be disclosed only 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 US Food and Drug Administration (FDA), the China National Medical Products Administration (NMPA), the European Medicines Agency (EMA), and all other national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC 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 Investigator's Brochure, this protocol, CRFs, the IND, 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.

13.5. Financial Disclosure

Investigators are required to provide the Sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. 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).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collections and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator must provide e-signature in the EDC system to attest to its accuracy, authenticity, and completeness.

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

14.1.2. Data Management/Coding

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

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

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

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

All AEs will be coded using the MedDRA® Dictionary Version 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA® Dictionary

14.2. Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the unblinded patient level clinical data in the EDC system will be assigned to predefined study personnel only. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs or the unblinded data from the EDC system with other functions/persons who do not have access to the EDC. Although the trial is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. PD-L1 status of each

individual patient will be blinded to the Sponsor, site and patient whenever feasible in order to avoid unwanted bias. A procedure of capping PD-L1 negative subset at 60% of the ITT Analysis Set (see Section 1.5.5) will be described in a Data Integrity Protection Plan. More details of in-house blinding are provided in the Data Integrity Protection Plan.

14.3. Study Records Retention

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

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

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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

The Sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the Sponsor's standards/procedures; otherwise, the retention period will default to the 15 years.

The investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

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

14.4. Protocol Deviations

The investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

The investigator should document and explain any deviations from the approved protocol. The investigator should promptly report any major deviations that might impact patient safety or data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

14.5. Publication and Data Sharing Policy

A Clinical Study Report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of BeiGene (Sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. For multicenter studies, 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 2016.

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

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the Sponsor prior to submission. 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 details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

14.6. Study and Study Center Closure

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

- Return of all study data to the Sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the Sponsor
- Shipment of PK samples to assay laboratories

In addition, the Sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the Sponsor determines such action is needed, the Sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

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

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

14.7. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the Sponsor, and are hereby assigned to the Sponsor.

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

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor and will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose in order to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.5

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

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3			Cycle 4 and Subsequent cycles (Every 21 days)	End of Treatment Visit[2]		
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 days**	**30 ± 7 days after last dose**	**Every 3 months**
Informed consent[1,18]	X							
Inclusion/exclusion criteria	X							
Randomization		X[23]						
Demographic/Medical history[5]	X							
Vital signs/Height/Weight[6]	X	X	X	X	X	X	X	
Physical examination[25]	X	X	X	X	X	X	X	
ECOG PS	X	X			X	X	X	
12-lead ECG[7]	X	as clinically indicated					X	
Adverse events[8]	X	X	X	X	X	X	X[8]	X[8]
Concomitant medications	X	X	X	X	X	X	X	
CBC with differential[9]	X[1]	X	X	X	X	X	X	
Serum chemistry[9]	X[1]	X	X	X	X	X	X	
CK and CK-MB[24]	X	X	X	X	X	X	X	
Urinalysis[9]	X	As clinically indicated[2,9]						
Coagulation[9]	X	As clinically indicated [2,9]						
Anti-tislelizumab antibodies[10]		X			X		X	
Pregnancy test[11]	X	X			X			

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3			Cycle 4 and Subsequent cycles (Every 21 days)	End of Treatment Visit[2]		
Days (window)	**-28 to -1**	**1 (± 3)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**0 to 7 days**	**30 ± 7 days after last dose**	**Every 3 months**
Thyroid function[12]	X[1]				X		X	
Pharmacokinetics[13]		X			X		X	
HBV/HCV tests[14]	X	as clinically indicated						
Tumor assessment[15]	X	tumor assessment starts 9 weeks after randomization						
Brain MRI/CT[15]	X	as clinically indicated						
Bone scan[16]	X	as clinically indicated						
Archival/Fresh tumor tissues collection[17]	X[1]							
Study drug administration[18]		X			X			
EQ-5D-5L[19]		X			X	X		
EORTC QLQ-C30[19]		X			X	X		
EORTC QLQ-LC 13[19]		X			X	X		
Survival status[4]								X
Pulmonary function tests[20]	X							
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[21,22]	X				X[21]	X[22]	X[22]	

Abbreviations: ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; ALK = anaplastic lymphoma kinase; CBC = complete blood count; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; EORTC QLQ-LC 13 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer-13 Questions; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L = 5-level European Quality of Life 5-Dimensions (health questionnaire); EOT = End of Treatment; FFPE = formalin-fixed paraffin-embedded; HBcAB = hepatitis B core antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; irAE = immune-related adverse event; IV = intravenously; NCI-CTCAE = National Cancer Institute Common

Toxicity Criteria for Adverse Events; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; PS = performance status; Q3W = once every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid stimulating hormone; X = to be performed

1. Written informed consent must be required for 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 randomization may be used for screening assessments rather than repeating such tests. Fresh tumor biopsy is permitted to be conducted up to 42 days prior to Cycle 1 Day 1, if no archival tumor tissue is available.
2. The EOT Visit is defined as the day that the investigator determines that tislelizumab or docetaxel will no longer be administered to a patient. If routine laboratory tests (hematology, serum chemistry, etc.) are completed within 7 days before the EOT Visit, tests need not be repeated. The tumor assessment is not required at the EOT Visit provided that fewer than 6 weeks have passed since the last assessment
3. The Safety Follow-up Visit should be conducted 30 days (±7 days) after the last dose of study treatment or before the initiation of a new anticancer treatment whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1, baseline, or stabilization. In addition, telephone contacts with patients should be conducted to assess immune-related AEs and concomitant medications (if appropriate, ie, associated with an immune-related AE) at 60 days (±14 days), and 90 days (±14 days) after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-related AE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.
4. Survival follow-up information and anticancer treatment will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months or at the Sponsor's request, until death, loss to follow-up, withdrawal of consent, or study termination by Sponsor. All patients will be followed for survival unless the patient requests to be withdrawn from follow-up.
5. Includes age or date of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Radiographic studies performed prior to study entry may be collected for review by the investigator.
6. Vital signs include resting temperature (°C), pulse and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. For the first infusion, the patient's vital signs should be determined within 60 minutes before the infusion and 30 minutes after the infusion. For subsequent infusions, vital signs should be collected with 60 minutes before the infusion and if clinically indicated, during and 30 minutes after the infusion. Height should only be measured and recorded at baseline. Pulse oximetry should be obtained at rest and with exercise at baseline and to be repeated as clinically indicated while on study; see also footnote #20 regarding pulmonary function testing.
7. ECG recordings will be obtained during screening, Safety Follow-up and as clinically indicated at other time points. Patients should be resting for at least 10 minutes prior to ECG collection.
8. The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 4.03. All AEs will also be evaluated for seriousness. After informed consent has been signed, but prior to the administration of the study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after the last dose of either study treatment or initiation of a new anticancer therapy, whichever occurs first. Immune-related AEs (serious and non-serious) will be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs should be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.
9. Laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Section 7.4.4. If hematology and serum chemistry tests at screening are not performed within 7 days of Cycle 1 Day 1, these tests should be repeated and reviewed before Cycle 1 Day 1. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 3 cycles and then at the beginning of subsequent cycles (data collected as specified in Section 7.4.4). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Urinalysis and coagulation laboratory tests are to be conducted during the treatment period only if clinically warranted. Refer to Section 8.4.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[10] ADA samples will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform ADA sampling and handling. Blood for anti-tislelizumab antibodies should be collected within 60 minutes before start of infusion (predose) on Day 1 of Cycles 1, 2, 5, 9, 17, and at the mandatory Safety Follow-up Visit. All samples should be drawn at the same time as blood collection for PK predose sampling.

[11] Urine or serum pregnancy test (for women of childbearing potential, including premenopausal 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.

[12] Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc.), and at the Safety Follow-up Visit. Values within 28 days of randomization are acceptable.

[13] PK samples will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform PK sampling and handling. For tislelizumab, predose (within 60 min before start infusion) samples should be collected at Day 1 of Cycle 1, 2, 5, 9 and 17; postdose (within 30 min after the end of infusion) samples should be collected at Day 1 of Cycle 1 and Cycle 5. An additional PK sample should be collected at the mandatory Safety Follow-up Visit. If a patient presents with any ≥ Grade 3 irAE, additional blood PK samples may be taken to determine the serum concentration of tislelizumab.

[14] Testing will be performed at screening and as clinically indicated, including HBsAg, HBcAb, and HCV antibody. Patients who are HBsAg positive or HCV antibody positive at screening must not be enrolled until further definitive testing results show HBV DNA titres <500 IU/mL (or 2500 copies/mL), or HCV RNA polymerase chain reaction test is negative, respectively.

[15] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of randomization may be used rather than repeating tests, provided they meet screening requirements. Brain imaging should be obtained within 28 days of randomization, but ideally within 14 days of randomization. All measurable and evaluable lesions should be assessed and documented at the Screening Visit and need to be reassessed at each subsequent tumor evaluation. 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 (± 7 days) during Year 1, every 12 weeks (± 7 days) from Year 2 onwards based on RECIST v1.1. Patients who discontinue from treatment for reasons other than disease progression (eg, toxicity) will continue the tumor assessments as scheduled until disease progression, withdrawal of consent, lost to follow-up, death, or start of a new anticancer therapy. Investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who continue tislelizumab beyond radiographic disease progression will be monitored with a follow-up scan at no more than 6 to 8 weeks beyond the initial diagnosis of PD before discontinuation of tislelizumab. See also Section 7.5 for further details.

[16] If performed within 3 months of randomization, it is not required to be repeated.

[17] Patients must be able to provide archival/fresh tumor tissues (FFPE blocks or approximately 11 [at least 5] freshly cut unstained FFPE slides) for biomarker analysis to assess PD-L1 expression and, provided sufficient tissue, including tumor mutational burden (TMB), gene expression profiling (GEP), and tumor-infiltrating immune cells. Documentation of wild type status of EGFR by tissue-based test must be provided for patients with non-squamous NSCLC prior to enrolment. For undocumented cases, archival/fresh tumor tissues (FFPE blocks or 6 freshly cut unstained FFPE slides) are required for central assessment of EGFR mutation. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 42 days before Cycle 1 Day 1) is mandatory (written informed consent is required prior to fresh tumor biopsies).

[18] Tislelizumab will be given IV every three weeks for patient in Arm A. Treatment could continue beyond progression at the investigator's discretion if pseudo-progression is suspected and/or if there is reasonable belief that the patient could continue to derive benefit, and as long as criteria defined in Section 7.5 are met. The patient should sign an informed consent form for continued treatment beyond RECIST v1.1. Docetaxel will be given IV every three weeks for patients in Arm B until disease progression. Cross-over to tislelizumab is not allowed for docetaxel arm.

[19] To be completed prior to any clinical activities during on study site visits.

[20] Pulmonary function testing including spirometry and assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity, are to be performed for all patients during the Screening Period to assist the determination of suitability on the study.

Respective test results need to be submitted to the Sponsor. Refer to Section 7.1.4 for further details. Tests may be repeated as clinically indicated while on study.

[21.] For tislelizumab arm only: Eye exam, visual acuity test, and optical coherence tomography (OCT; or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. Eye exam, visual acuity test, and OCT (or equivalent diagnostic test) will be assessed by an appropriate specialist at the Screening Visit. Patients treated with tislelizumab will undergo repeat assessments approximately every 15 weeks (± 7 days).

[22.] To be performed only once at either the EOT or during safety follow up, within 30 days of study treatment end in patients treated with tislelizumab.

[23.] Patients will be randomized into either the tislelizumab or docetaxel via IRT. All patients are required to receive study treatment within 2 business days of randomization.

[24.] All patients will have creatine kinase (CK) and creatine kinase-cardiac muscle isoenzyme (CK-MB) testing at screening, and to be repeated at predose assessments in all treatment cycles, and other scheduled visits during the first 3 treatment cycles, and at the end of treatment and safety follow up visits. (In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.) Refer to Section 8.4.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[25.] A complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.4.2). Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during tislelizumab treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.

APPENDIX 2. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

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 (v1.1). 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.

Nonmeasurable 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 nonmeasurable 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 nonmeasurable

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 subjected to other loco-regional 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, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 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 nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological 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.

Nontarget 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 nontarget 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 prostate-specific antigen 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.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (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 Nontarget Lesions

While some nontarget 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.

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget 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 3 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 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 nontarget 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	Nontarget 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

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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".

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 nonrandomized 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 randomized 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 2 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 3. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

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

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment).
  - NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR

- < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

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

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

APPENDIX 5. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

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

APPENDIX 6. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1] 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.

This CKD-EPI equation calculator should be used when Scr is 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/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12).

APPENDIX 7. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune related AE are intended as a guidance. This document should be used in conjunction with expert clinical judgment (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 DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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

Treatment of Immune-related Adverse Events

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	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 Judgment)	Study Drug Management
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. 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 $\leq$ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.

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

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

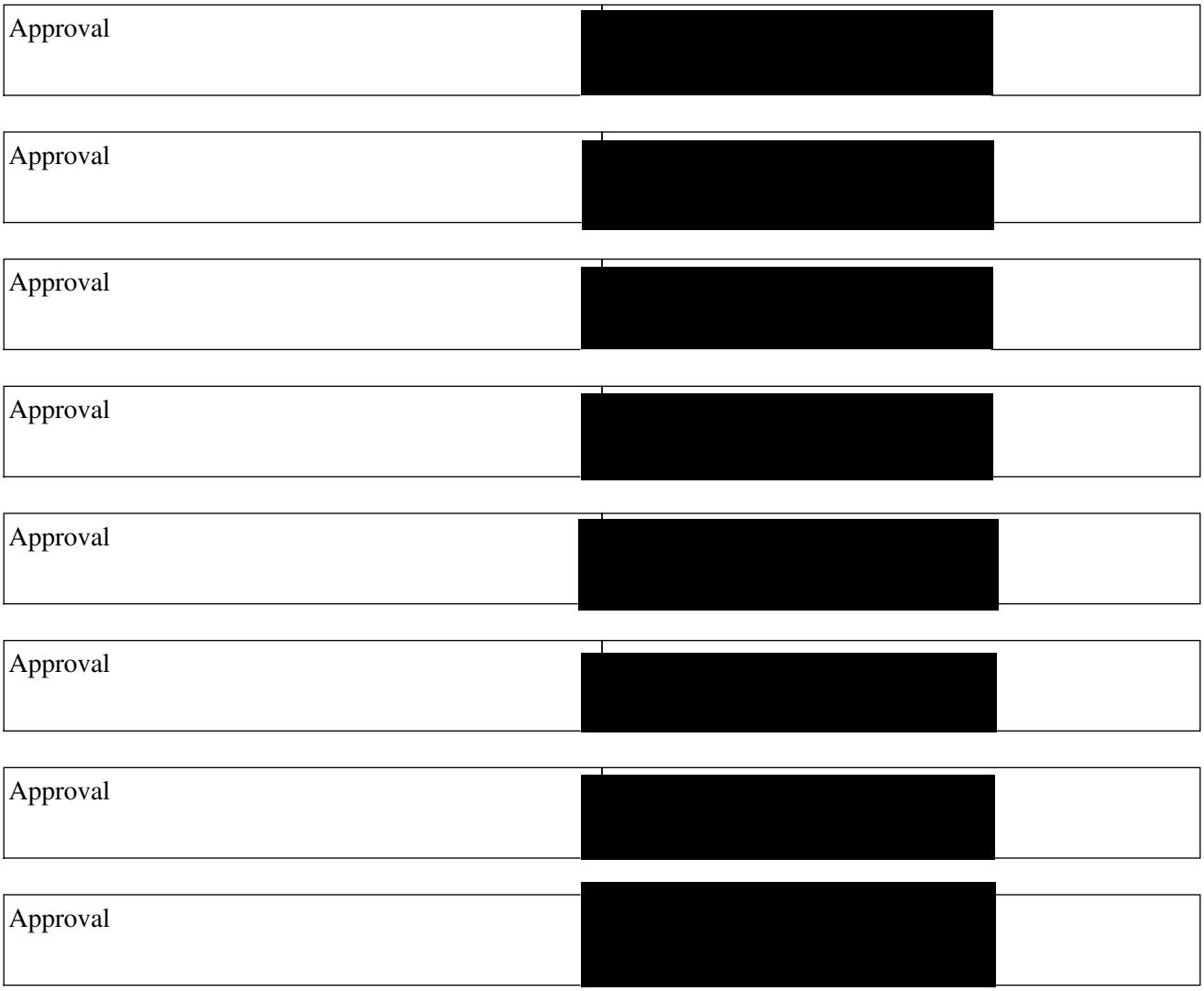
Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: 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 or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
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.	Hold study treatment; reintroduce only after discussion with the

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
		Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	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 complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3X ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	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 cardiac testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1 2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CHF, congestive heart failure; CK, creatine kinase; CK-MB, creatine kinase cardiac isoenzyme; 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.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