CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer
Protocol Identifier:	BGB-A317-304
Phase:	3
Investigational Product(s):	Tislelizumab (BGB-A317)
Indication:	Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer
Sponsor:	**BeiGene (Shanghai) Co., Ltd.** Floor 4, Building D No. 780, Cailun Road Pilot Free Trade Zone Shanghai 201203, P.R. China
Sponsor Medical Monitor:	[redacted]
Original Protocol:	11 January 2018
Amendment 1.0:	07 June 2018
Amendment 2.0:	24 January 2019

FINAL PROTOCOL APPROVAL SHEET

Protocol Title: A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer

BeiGene (Shanghai) Co., Ltd., Approval:

[redacted]	Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed Alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer

Protocol Identifier: BGB-A317-304

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene (Shanghai) Co., Ltd., or one of its subsidiaries.

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. Return the signed copy to BeiGene or its designee.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

TABLE OF CONTENTS

CLINICAL STUDY PROTOCOL **1**
FINAL PROTOCOL APPROVAL SHEET **2**
INVESTIGATOR SIGNATURE PAGE **3**
TABLE OF CONTENTS **4**
LIST OF TABLES **10**
LIST OF FIGURES **11**
PROTOCOL AMENDMENT, VERSION 2.0, RATIONALE **12**
SYNOPSIS **14**
LIST OF ABBREVIATIONS AND TERMS **24**
1 INTRODUCTION **26**
1.1 Background Information on Non-Small Cell Lung Cancer 26
1.2 Current First-Line Treatment of NSCLC 26
1.2.1 First-Line Treatment for Advanced NSCLC With an *EGFR* Mutation or *ALK* Rearrangement 26
1.2.2 First-Line Treatment for Advanced NSCLC Without an *EGFR* Mutation or *ALK* Rearrangement 27
1.2.3 Platinum-Based Regimen for First-Line NSCLC 27
1.2.4 Pemetrexed-Based Regimen for First-Line NSCLC 28
1.2.5 Targeted Therapy for NSCLC 29
1.2.6 Anti-PD-1/Anti-PD-L1 Therapy for Advanced NSCLC 30
1.3 Unmet Medical Needs for First-Line NSCLC 34
1.4 Background Information on Tislelizumab 35
1.4.1 Pharmacology 35
1.4.2 Toxicology 35
1.4.3 Clinical Pharmacology 36
1.4.4 Prior Clinical Experience of Tislelizumab 36
1.5 Study Rationales 39
1.5.1 Rationale for the Chemotherapy Regimens Administered With Tislelizumab in the Treatment of Advanced Non-Squamous NSCLC 39

1.5.2 Rationale for Selection of Tislelizumab Dose in Combination With Chemotherapy 40
1.5.3 Rationale for Platinum Doublet Chemotherapy as the Comparator .41
1.5.4 Rationale for Primary Endpoint of PFS as Assessed by the IRC 41
1.5.5 Rationale for Requiring PD-L1 Testing....41
1.5.6 Rationale for Allowing Crossover to Tislelizumab 42
1.5.7 Rationale for Allowing Patients to Continue Tislelizumab Containing Treatment Until Loss of Clinical Benefit....42
1.5.8 Rationale for Patient-Reported Outcome Assessments 42
1.6 Benefit-Risk Assessment 43
2 STUDY OBJECTIVES AND ENDPOINTS.....44
2.1 Study Objectives 44
2.1.1 Primary Objective 44
2.1.2 Secondary Objectives.....44
2.1.3 Exploratory Objectives 44
2.2 Study Endpoints 45
2.2.1 Primary Endpoint 45
2.2.2 Secondary Endpoints 45
2.2.3 Exploratory Endpoints 45
3 STUDY DESIGN.....46
3.1 Summary of Study Design 46
3.2 Screening Period 49
3.3 Treatment Period.....49
3.4 Safety Follow-up.....51
3.5 Survival Follow-up 51
3.6 Discontinuation From the Study Treatment or From the Study 52
3.6.1 Discontinuation from Study Treatment 52
3.6.2 Patient Discontinuation From Study (End of Study for an Individual Patient).....52
3.7 End of Study 52
4 STUDY POPULATION 53
4.1 Inclusion Criteria 53
4.2 Exclusion Criteria 54

5 STUDY TREATMENT 57
5.1 Formulation, Packaging, and Handling 57
5.1.1 Tislelizumab 57
5.1.2 Chemotherapy Agents 58
5.2 Dosage, Administration, and Compliance 58
5.2.1 Tislelizumab 59
5.2.2 Chemotherapy 59
5.3 Overdose 60
5.4 Investigational Medicinal Product Accountability 60
5.5 Dose Delay or Modification 60
5.5.1 General Guidance Regarding Dose Modifications 61
5.5.2 Dose Delay or Modification for Tislelizumab 62
5.5.3 Dose Delay or Modifications for Chemotherapy Treatment 62
5.6 Criteria for Discontinuing Chemotherapy Regimens 63
6 PRIOR AND CONCOMITANT THERAPY 64
6.1 Prior Therapy 64
6.2 Concomitant Therapy 64
6.2.1 Permitted Concomitant Medications/Procedures 64
6.2.2 Prohibited Concomitant Medications/Procedures 65
6.2.3 Restricted Concomitant Medications/Procedures 66
6.3 Potential Interactions Between the Study Drugs and Concomitant Medications 66
7 STUDY ASSESSMENTS AND PROCEDURES 66
7.1 Screening 66
7.1.1 Demographic Data and Medical History 67
7.1.2 Females of Childbearing Potential and Contraception 67
7.1.3 Informed Consent and Screening Log 67
7.1.4 Pulmonary Function Tests 68
7.2 Enrollment 68
7.2.1 Confirmation of Eligibility 68
7.2.2 Patient Numbering 68
7.2.3 Randomization 68

7.3 Tislelizumab and Chemotherapy Dispensation 68
7.4 Crossover 69
7.4.1 Crossover for Patients in Chemotherapy in Arm B With Documented and IRC Confirmed Disease Progression 69
7.4.2 Crossover Assessments and Procedures 69
7.5 Safety Assessments 70
7.5.1 Vital Signs 70
7.5.2 Physical Examinations 70
7.5.3 Eastern Cooperative Oncology Group Performance Status 71
7.5.4 Laboratory Safety Tests 71
7.5.5 Electrocardiograms 72
7.5.6 Adverse Events 72
7.5.7 Hepatitis B and C Testing 72
7.6 Tumor and Response Evaluations 73
7.7 Pharmacokinetic and Antidrug Antibody Testing 74
7.8 Biomarkers 75
7.9 Patient-Reported Outcomes 76
7.10 Visit Windows 76
7.11 Unscheduled Visits 76
8 SAFETY MONITORING AND REPORTING 76
8.1 Risks Associated With Study Drug 76
8.1.1 Risks Associated With Tislelizumab 76
8.1.2 Risks Associated With Cisplatin/Carboplatin and Pemetrexed 77
8.2 General Plan to Manage Safety Concerns 77
8.2.1 Eligibility Criteria 77
8.2.2 Safety Monitoring Plan 78
8.3 Adverse Events 78
8.3.1 Definitions and Reporting 78
8.3.2 Assessment of Severity 79
8.3.3 Assessment of Causality 79
8.3.4 Following Adverse Events 80
8.3.5 Laboratory Test Abnormalities 81

8.4 Definition of a Serious Adverse Event 82
8.5 Suspected Unexpected Serious Adverse Reaction....82
8.6 Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events 83
8.6.1 Adverse Event Reporting Period 83
8.6.2 Reporting Serious Adverse Events 83
8.6.3 Eliciting Adverse Events....84
8.6.4 Recording Disease Progression....84
8.6.5 Deaths 84
8.6.6 Pregnancies 85
8.6.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees..85
8.6.8 Assessing and Recording Immune-Related Adverse Events 85
8.7 Management of AE of Special Interest....85
8.7.1 Infusion-Related Reactions....86
8.7.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms....87
8.7.3 Immune-Related Adverse Events 88
8.7.4 Renal Function Abnormalities 89
9 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION....89
9.1 Statistical Analysis....89
9.1.1 Randomization Methods 89
9.1.2 Analysis Sets....90
9.1.3 Patient Disposition....90
9.1.4 Demographic and Other Baseline Characteristics 90
9.1.5 Prior and Concomitant Medications 90
9.2 Efficacy Analyses 91
9.2.1 Primary Efficacy Analysis 91
9.2.2 Secondary Efficacy Analysis 92
9.2.3 Exploratory Efficacy Analysis....93
9.3 Safety Analyses....94
9.3.1 Extent of Exposure....94
9.3.2 Adverse Events 94
9.3.3 Laboratory Analyses 94

9.3.4 Vital Signs....95
9.4 Pharmacokinetic Analysis....95
9.5 Sample Size Consideration....95
9.6 Interim Analyses....96
9.7 Immunogenicity Analyses....96
10 STUDY COMMITTEES AND COMMUNICATION....96
10.1 Blinded Independent Central Review....96
10.2 Independent Data Monitoring Committee....97
11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS97
11.1 Access to Information for Monitoring....97
11.2 Access to Information for Auditing or Inspections....98
12 QUALITY ASSURANCE AND QUALITY CONTROL....98
12.1 Regulatory Authority Approval....98
12.2 Quality Assurance....98
12.3 Study Site Inspections....98
12.4 Drug Accountability....98
13 ETHICS/PROTECTION OF HUMAN PATIENTS....99
13.1 Ethical Standard....99
13.2 Institutional Review Board/Independent Ethics Committee....99
13.2.1 Protocol Amendments....100
13.3 Informed Consent....100
13.4 Patient and Data Confidentiality....100
13.5 Financial Disclosure....101
14 DATA HANDLING AND RECORD KEEPING....101
14.1 Data Collection and Management Responsibilities....101
14.1.1 Data Collection....101
14.1.2 Data Management/Coding....102
14.2 Data Integrity and In-house Blinding....102
14.3 Study Records Retention....102
14.4 Protocol Deviations....103
14.5 Publication and Data-Sharing Policy....104
14.6 Study and Study Center Closure....105

14.7 Information Disclosure and Inventions....105

15 REFERENCES....107

APPENDIX 1. SCHEDULE OF ASSESSMENTS....115

APPENDIX 2. ECOG PERFORMANCE STATUS....120

APPENDIX 3. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1....121

APPENDIX 4. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES....131

APPENDIX 5. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION....132

APPENDIX 6. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT....133

APPENDIX 7. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION....143

APPENDIX 8. COCKCROFT-GAULT FORMULA AND CALVERT FORMULA...144

APPENDIX 9. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"....145

APPENDIX 10. DOSE MODIFICATION OF CHEMOTHERAPY....147

LIST OF TABLES

Table 1. Selection and Timing of Dose for Each Patient....59

Table 2. The Summary of the Commonly and Specific Reported Toxicity of the Chemotherapeutic Agents....77

Table 3. Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee....83

Table 4. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)....86

Table 5. Immune-Related Adverse Events....88

Table 6. Analysis Timing and Stopping Boundary for PFS in the ITT Analysis Set (overall one-sided hypothesis testing at $\alpha = 0.025$)....96

Table 7. Chemotherapy Dose Modification[1] for Hematological Toxicity....147

Table 8. Chemotherapy Dose Modifications for Non-Hematological Toxicity....148

LIST OF FIGURES

Figure 1. Study Schema 48

PROTOCOL AMENDMENT, VERSION 2.0, RATIONALE

The main purpose of this protocol amendment is:

- To clarify the operational details of serum creatinine kinase (CK) and creatinine kinase cardiac muscle isoenzyme (CK-MB) testing for close monitoring of myocarditis/myositis;
- To update myocarditis/myositis language (immune-related adverse event evaluation and management) according to FDA requirements;
- To update to allow subjects with PD-L1 unevaluated results to be included in this study;
- To update the procedures for select study assessments to allow for greater flexibility in keeping with clinical practice;
- To revise the content for clarity and consistency to align with the latest updates to the tislelizumab protocol template, including updates to safety assessment.

Further, administrative modifications (eg, typos, format changes, add or delete abbreviations, etc.) were made to improve upon the clarity and consistency throughout the document. And the synopsis was updated to match changes made in the body of the protocol. The version number of this protocol amendment is 2.0.

Key changes made from the Protocol Amendment 1.0 (dated 07 June 2018) to Protocol Amendment 2.0 (dated 24 January 2019), are summarized by protocol section as below:

- In Section 2.1.1, Primary Objective: added ‘American Joint Committee Cancer 7th Edition of Cancer Staging Manual’ for clarification;
- In Section 3.1, Summary of Study Design, Section 4.1, Inclusion Criteria, and Section 7.8, Biomarkers: allowed patients with unevaluable PD-L1 status to participate in this study with the purpose of expanding the scope of study population who are likely to benefit from the study treatment;
- In Section 3.1, Summary of Study Design and Section 5.2.2, Chemotherapy: updated the duration of administration for carboplatin to be consistent with the information in its respective label;
- In Section 4.2, Exclusion Criteria and Section 7.5.7, Hepatitis B and C Testing: further specified the exclusion criteria for patients with infections, active hepatitis C virus, hearing impairment, and peripheral neuropathy;
- In Section 7.1, Screening and Section 7.1.4, Pulmonary Function Tests:
  - clarified that pulmonary function testing at screening should, in addition to spirometry, include assessment of oxygenation, at a minimum pulse oximetry at rest and with exercise, or alternatively, assessment of diffusion capacity.
  - added the guidance on the assessment of pulmonary function in all patients during the screening period;

- In Section 7.4.2, Crossover Assessments and Procedures: clarified the safety assessment schedule for patients who cross over to tislelizumab monotherapy;
- In Section 7.5, Safety Assessments: further specified the venue of Day 1 visits and allowed for greater flexibility for AEs and concomitant medications on Day 8 and Day 15;
- In Section 7.5.4, Laboratory Safety Test: clarified the assessment schedule of hematology and serum chemistry testing, especially serum CK and CK-MB;
- In Section 7.6, Tumor and Response Evaluations: updated screening assessments for flexibility and clarified reassessment time of patient with known and previously treated brain metastases;
- In Section 7.8, Biomarkers, Appendix 1, Schedule of Assessments: clarified collection time for blood biomarker;
- In Section 8.3.3, Assessment of Causality: updated for consistency with other BeiGene protocols；
- In section 8.3.5, Laboratory Test Abnomalities: added more text about laboratory test abnormalities related AE for clarification;
- In Section 9, Statistical Methods and Sample Size Determination: deleted the text of SAS® Version that is included in the statistical analysis plan;
- In Section 9.2.2, Secondary Efficacy Analysis: updated statistical analysis method for health-related quality of life;
- In Section 9.3.2, Adverse Events: updated the wording of AE reporting window for consistency with wording in section 8.2.2 and 8.6.1;
- In Appendix 1, Schedule of Assessments: added details for consistency with the text in the protocol and other BeiGene protocols, corrected assessment timepoint for EORTC QLQ-C30, and EORTC QLQ-LC13;
- In Appendix 8, Cockcroft-Gault Formula and Calvert Formula: added the calculation details for the dose of carboplatin to avoid potential toxicity due to overdosing.

SYNOPSIS

Name of Sponsor/Company: BeiGene (Shanghai) Co., Ltd.
Investigational Product: Tislelizumab (BGB-A317) Injection
Title of Study: A Phase 3, Open-Label, Multicenter, Randomized Study to Investigate the Efficacy and Safety of Tislelizumab (BGB-A317) (Anti-PD1 Antibody) Combined With Platinum-Pemetrexed Versus Platinum-Pemetrexed alone as First-line Treatment for Patients With Stage IIIB or IV Non-Squamous Non-Small Cell Lung Cancer
Protocol Identifier: BGB-A317-304
Phase of Development: 3
Number of Patients: 320
Study Centers: Approximately 40-45 centers

Study Objectives:

Primary:

- To compare the progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in an Intent-To-Treat (ITT) analysis set between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in chemotherapy-naive patients with Stage IIIB or Stage IV (as classified according to American Joint Committee Cancer 7th edition of Cancer Staging Manual) non-squamous, non-small cell lung cancer (NSCLC).

Secondary:

- To compare overall response rate (ORR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To compare duration of response (DOR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To compare overall survival (OS) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in an ITT analysis set.
- To compare PFS as assessed by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in an ITT analysis set.
- To compare health-related quality of life (HRQoL) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To evaluate the safety and tolerability of tislelizumab combined with platinum-pemetrexed compared with platinum-pemetrexed alone.
- To evaluate the correlation between programmed death-ligand 1 (PD-L1) expression levels by immunohistochemistry (IHC) and antitumor activity of tislelizumab combined with platinum-pemetrexed alone.

Exploratory:

- To compare tumor assessment outcomes (eg, disease control rate [DCR], time to response [TTR]) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone as assessed by the investigator per RECIST v1.1.
- To assess tumor and blood biomarkers of tislelizumab response, resistance, and patient prognosis.
- To characterize the pharmacokinetics of tislelizumab when given in combination with platinum-pemetrexed.
- To assess host immunogenicity to tislelizumab

Study Endpoints:

Primary:

- PFS as assessed by the IRC–the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in an ITT analysis set.

Secondary:

- ORR as assessed by the IRC–the proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in ITT analysis set.
- DOR as assessed by the IRC–the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the IRC per RECIST v1.1 in ITT analysis set with documented objective responses.
- OS–the time from the date of randomization to the date of death due to any cause in an ITT analysis set.
- PFS as assessed by the investigator–the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1 in an ITT analysis set.
- ORR as assessed by the investigator–the proportion of patients who had CR or PR as determined by the investigator per RECIST v1.1 in ITT analysis set.
- DOR as assessed by the investigator–the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as determined by the investigator per RECIST v1.1 in ITT analysis set with documented objective responses.
- HRQoL–measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ LC13) and Core 30 (EORTC QLQ-C30) as presented in patient-reported outcomes.
- Incidence and severity of treatment-emergent AEs (TEAEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0.
- PD-L1 expression by IHC as a predictive biomarker for response.

Exploratory:

- DCR–the proportion of patients who had complete response (CR), partial response (PR), or stable disease (SD) as assessed by the investigator per RECIST v1.1.

- Time to response (TTR)–the time from randomization to the first occurrence of a documented objective response per RECIST v1.1.
- Status of exploratory biomarkers including but not limited to PD-L1 expression, tumor mutation burden (TMB), and immune-related gene expression profiling (GEP) in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) obtained before, during, or after treatment with tislelizumab or at progression, and the association with disease status and/or response to tislelizumab in combination with chemotherapy.
- Summary of serum concentrations of tislelizumab.
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADAs).

Study Design:

This is an open-label, randomized, multicenter, Phase 3 study designed to compare the efficacy and safety of tislelizumab combined with cisplatin or carboplatin + pemetrexed (Arm A) and cisplatin or carboplatin + pemetrexed alone (Arm B) as first-line treatment in approximately 320 patients who have Stage IIIB or IV non-squamous NSCLC, whereby choice of platinum (cisplatin or carboplatin) will be at the investigator's discretion.

The study design schema is in Section 3, Figure 1.

- Cisplatin 75 mg/m^2 administered as an intravenous (IV) infusion over 2 hours Q3W (every 3 weeks) for 4 to 6 cycles
- Carboplatin AUC 5 administered as an IV infusion over 15 minutes Q3W for 4 to 6 cycles
- Pemetrexed 500 mg/m^2 administered as an IV infusion over 10 minutes Q3W

The primary endpoint of the study is measured by PFS as assessed by the IRC in ITT analysis set.

Patients who have not received chemotherapy with histologically confirmed non-squamous, locally advanced or metastatic (Stage IIIB or IV) NSCLC are eligible. Histology of non-squamous NSCLC will be confirmed at the investigator's site. Patients with known *EGFR* mutation or ALK rearrangement are ineligible for the study; for patients without tissue-based *EGFR* status, fresh or archival tumor tissues are required for *EGFR* mutation assessment. Archival tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. If archived formalin-fixed paraffin-embedded (FFPE) tissue is not sufficient for PD-L1 analysis, a fresh biopsy sample will need to be obtained. PD-L1 status will be characterized as PD-L1 membrane staining on tumor cells (TC) via the Ventana SP263 assay.

Eligible patients will be stratified by tumor staging (IIIB versus IV) and PD-L1 expression (3 levels: < 1% TC versus 1%–49% TC versus ≥ 50% TC). Patients whose tissues are unevaluable for PD-L1 expression will be included in the < 1% TC group. All patients will be randomized by a 2:1 ratio to receive one of the following treatment regimens:

- Induction phase (4 to 6 cycles, Q3W):

  Arm A: tislelizumab + carboplatin or cisplatin + pemetrexed
  Arm B: carboplatin or cisplatin + pemetrexed

- Maintenance phase (Q3W):

  Arm A: tislelizumab + pemetrexed
  Arm B: pemetrexed

Selection of platinum will be determined by the investigator and documented prior to randomization.

The number of cycles of induction treatment (4 to 6) will be at the discretion of the investigator. Induction treatment will be administered on a 3-week cycle until 1 of the following occurs (whichever occurs first): 1) completed administration of 4 to 6 cycles; 2) unacceptable toxicity; or 3) documented disease progression per RECIST 1.1.

After the induction phase, patients who have not experienced disease progression or unacceptable toxicity will continue treatment with maintenance therapy. Patients randomized to either Arm A or Arm B will continue treatment with pemetrexed maintenance therapy until progressive disease, unacceptable toxicity, or death, whichever occurs first.

For all patients in Arm A, if progression of disease is unconfirmed and the patient is clinically stable, it is at the discretion of the investigator to continue the assigned study treatment per protocol until disease progression is confirmed at least 28 days (or at the next scheduled tumor assessment) from the date of the scan suggesting disease progression. If a patient has confirmed disease progression per RECIST v1.1, the patient should not receive further chemotherapy treatment on study, and should follow the following guidance:

<u>For Arm A (Experimental arm):</u>

Patients who experience progressive disease per RECIST v1.1 during chemotherapy combination phase (induction or maintenance phase) or thereafter while receiving tislelizumab monotherapy will be permitted to continue tislelizumab monotherapy provided they meet all the following additional criteria:

1. Evidence of clinical benefit as assessed by the investigator
2. Absence of symptoms and signs (including clinically significant worsening of laboratory values [eg, new, or worsening hypercalcemia]) indicating unequivocal progression of disease
3. No decline in Eastern Cooperative Oncology Group (ECOG) performance status (PS) that can be attributed to disease progression
4. Absence of tumor progression at critical anatomical sites (eg, central nervous system [CNS] disease) that cannot be managed by protocol-allowed medical interventions
5. Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

<u>For Arm B (Control arm):</u>

Patients randomized to Arm B who develop radiographic disease progression per RECIST v1.1 (to be confirmed by the IRC) will be given the option to cross over to receive tislelizumab monotherapy if they meet all the following criteria:

1. ECOG PS of ≤ 1
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, central nervous system [CNS] disease) that cannot be managed by protocol-allowed medical interventions
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen

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.

Crossover is optional and is at the discretion of the investigator and with the sponsor's agreement.

For Arm A and Arm B:

Once patients are receiving tislelizumab monotherapy, the investigator may consider continuing tislelizumab monotherapy beyond investigator-assessed progression, provided that patients meet the above outlined criteria, and upon discussion with the medical monitor.

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

A Steering Committee consisting of qualified investigators will be implemented to support the study and structure the scientific input.

Safety monitoring and interim efficacy data review will be performed by an Independent Data Monitoring Committee (IDMC). The first safety monitoring and review will occur after the first 30 patients recruited have been on treatment for at least 1 month or have completed at least 1 cycle of study treatment. Thereafter, IDMC will review data approximately every 6 months, or more frequently if indicated or requested by the medical monitor based on ongoing safety monitoring of patients on study. The IDMC may recommend study modification including early termination of the study due to safety concerns, or for evidence of compelling efficacy at a pre-planned interim analysis. A formal interim analysis for PFS in the ITT analysis set is planned when approximately 71% of the total targeted PFS events in the ITT analysis set have been observed. The early stopping rule for the interim analysis will be set for superiority. The function and membership of the IDMC will be described in the IDMC charter.

The study is open-labeled for tislelizumab in combination with chemotherapy. The results of PD-L1 expression will be blinded to patients, investigators, study site personnel, sponsor staff, and representatives of the sponsor.

Study Assessments:

Patients will undergo tumor assessments at baseline and every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remaining 6 months of Year 1, and after completion of the Week 52 tumor assessment, tumor assessment will continue every 12 weeks (± 7 days) based on RECIST v1.1, regardless of dose delays to manage toxicities. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1 or loss of clinical benefit (for tislelizumab-only patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study completion by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

Patients who discontinue treatment for reasons other than radiographic disease progression (eg, toxicity) will continue scheduled tumor assessments until radiographic disease progression per RECIST v1.1, withdrawal of consent, loss to follow-up, study completion by sponsor, death, or the start of a new anticancer therapy, whichever occurs first.

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

Patients will be evaluated for AEs and immune-related adverse events (irAEs) (all grades according to NCI-CTCAE v5.0). Serious AEs (SAEs) and any AE will be followed and documented until the event resolves, the investigators assess the event as stable, or the patient is lost to follow-up, whichever occurs first.

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 study treatment (including chemotherapy) or initiation of

new anticancer therapy, whichever occurs first. All irAEs (serious or non-serious) should be reported for 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. The investigator should report any SAEs that are believed to be related to tislelizumab treatment at any time after treatment discontinuation.
Duration of Patient Participation: The duration of the study from first enrolled patient to final analysis for PFS is estimated to be approximately 21 months.
Study Population: The study will enroll approximately 320 patients who meet the following inclusion/exclusion criteria at a 2:1 randomization ratio with approximately 214 patients in the tislelizumab treatment arm (tislelizumab combined with pemetrexed + platinum) and approximately 106 patients in the chemotherapy-alone treatment arm (pemetrexed + platinum).
Key Eligibility Criteria: The population under study is adult patients (18 to 75 years old on the day the patient voluntarily agrees to participate in the study) with histologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) non-squamous NSCLC. Patients with tumors of mixed non-small cell histology (squamous and non-squamous) are eligible if the major histological component is confirmed to be non-squamous. Patients must be able to provide fresh or archival tumor tissues (FFPE blocks or approximately 15 [at least 6] freshly cut unstained FFPE slides) with an associated pathological report. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. Patients with NSCLC tumors that harbor an EGFR-sensitizing mutation or ALK gene translocation are excluded. Written confirmation of wild-type EGFR based on a tissue-based test is required. For patients without documented wild-type EGFR, archival or fresh tumor tissues are required for EGFR mutation assessment prior to enrollment. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1. Patients must have at least one measurable lesion as defined per RECIST v1.1 and have had no prior systemic chemotherapy for metastatic NSCLC. Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of at least 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization. Patients who have received prior treatment with EGFR inhibitors or ALK inhibitors or therapies targeting PD-1 or PD-L1 are excluded. Patients must have a life expectancy of ≥ 12 weeks. Patients must have adequate organ function as indicated by the screening laboratory values (obtained within 7 days prior to randomization) described in Section 4.1.
Investigational Product, Dose, and Mode of Administration: Tislelizumab will be administered at a dose of 200 mg intravenously (IV) Q3W.
Reference Therapy, Dose, and Mode of Administration: Cisplatin 75 mg/m^2 will be administered as an IV infusion over 2 hours Q3W for 4 to 6 cycles Carboplatin AUC 5 will be administrated as an IV infusion over 15 minutes Q3W for 4 to 6 cycles Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W

Statistical Methods:

Analysis Sets:

The Intent-to-Treat (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 all efficacy analysis, including analyses of PFS and OS endpoints.

The Per-Protocol (PP) analysis set includes randomized patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations will be determined and documented before the database lock for the primary analysis.

The Safety analysis set includes all randomized patients who received at least 1 dose of any component of study drug; it will be the population for the safety analyses.

The PK analysis set includes all patients who receive at least 1 dose of tislelizumab per the protocol, for whom any post-dose PK data are available.

The immunogenicity (ADA) analysis set includes all patients who received at least 1 dose of tislelizumab for whom both baseline ADA and at least 1 post-baseline ADA results are available.

Primary Efficacy Endpoint Analysis:

PFS as assessed by the IRC:

PFS per the IRC is defined as the time from randomization to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurs first. PFS will be analyzed in the ITT analysis set. 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 without post-baseline tumor assessment will be censored at the time of randomization. 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 loss to follow-up. Patients who have a clinical determination of progression should undergo a CT/magnetic resonance imaging (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.

PFS per the IRC will be compared between tislelizumab with platinum-pemetrexed (Arm A) and platinum-pemetrexed alone (Arm B) in a stratified log-rank test at one-sided significance level α=0.025.

The null hypothesis to be tested is: H_0: PFS in Arm A $\leq$ PFS in Arm B

Against the alternative hypothesis: H_a: PFS in Arm A > PFS in Arm B

The p-value from a stratified log-rank test will be presented using stratification factors. The median PFS 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 (HR) between Arm A and Arm 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 as recorded in eCRF.

Subgroup analysis of the primary endpoint of PFS per the IRC will be conducted to determine whether the treatment effect is consistent across various subgroups. The HR estimates of PFS and its 95% CI will be estimated and plotted within each category of the following variables: PD-L1 expression by IHC in TC ($\geq$ 50% TC versus 1%-49% TC versus < 1% TC), Stage (IIIB versus IV), age ($\leq$ 65 versus > 65 years), gender (female versus male), ECOG PS (0 versus 1), and smoking status (Former versus Current versus Never).

The analysis of PFS per the IRC in the PP analysis set may be conducted as sensitivity analysis.

Secondary Efficacy Endpoint Analyses:

Overall survival

OS is defined as the time from randomization to death from any cause. OS will be analyzed in the ITT analysis set. Data for patients who are not reported as having died at the time of analysis will be censored at the date of last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization.

Similar methodology used to evaluate PFS per the IRC will be applied to OS analysis.

Progression-free survival per the investigator

PFS per the investigator is defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined per RECIST v1.1 in an ITT analysis set. Similar methodology used to evaluate PFS per the IRC will be applied to analysis of PFS per the investigator.

Overall response rate per the IRC

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment will be considered non-responders. The difference in ORR between arms in the ITT analysis set will be evaluated using the Cochran-Mantel-Haenszel (CMH) 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.

Overall response rate per the investigator

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had a CR or PR as determined by the investigator per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment will be considered nonresponders. Similar methodology used to evaluate ORR per the IRC will be applied to analysis of ORR per the investigator.

Duration of response per the IRC

DOR per the IRC is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as assessed by the IRC using the RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

Duration of response per the investigator

DOR per the investigator is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator using the RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first

occurrence of the objective response. Similar methodology used to evaluate DOR per the IRC will be applied to analysis of DOR per the investigator.

Health-Related Quality of Life (HRQoL)

European Organization for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-LC13 and EORTC QLQ-C30) post-baseline 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 functional/symptom scales of both C30 and LC13 will be summarized descriptively.

PD-L1 expression as a predictive biomarker for response

PD-L1 expression will be examined in the ITT analysis set. Association between PD-L1 expression and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, DCR) will be explored.

Exploratory Efficacy Analyses:

Disease control rate per the investigator

DCR is defined as the proportion of patients with objective response (CR or PR) or stable disease (SD) maintained for ≥ 6 weeks as determined by the investigator using the RECIST v1.1. The analysis methods for DCR will be the same as those for ORR per the investigator.

Time to response (TTR) per the investigator

TTR per the investigator is defined for patients with an objective response as determined by the investigator as the time from randomization to the first occurrence of a CR or PR as determined by the investigator using the RECIST v1.1. TTR will be summarized for descriptive purposes. The mean, standard error, median, and range of TTR will be provided.

Safety Analyses:

Safety will be assessed by monitoring and recording all AEs graded by NCI-CTCAE v5.0. 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.

Sample size considerations:

The sample size calculation is based on the number of events required to demonstrate the PFS superiority of Arm A to Arm B in the ITT analysis set.

The estimates of the number of events required to demonstrate efficacy with regard to PFS in the primary comparisons are based on the following assumptions:

1. Median PFS of 7 months in Arm B with exponential distribution assumption.
2. At a one-sided α of 0.025, 85% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 7 months to 10.8 months, in the ITT analysis set.
3. Randomization ratio of 2:1.
4. One interim analysis of PFS planned in the ITT analysis set when approximately 71% of total PFS events occurred, with Lan-DeMets' approximation to O'Brien-Fleming boundary.

With these assumptions, a total of 215 PFS events is required for the ITT analysis set for the PFS final analysis. Assuming 320 patients are to be enrolled over an 8-month period at a constant enrollment rate, the PFS final analysis will occur approximately 19.2 months after the first patient is randomized.

Interim Analyses:

There will be one interim efficacy analysis of PFS performed in the ITT analysis set. The interim efficacy analysis of PFS will be performed when approximately 153 PFS events (71% of the targeted number of 215 PFS events) are observed in the ITT analysis set. It is estimated that it will take approximately 12.8 months to observe 153 PFS events.

The interim boundary for PFS is based on the Lan-DeMets approximation to O'Brien-Fleming boundary. The interim and final analysis timing, and stopping boundaries are summarized in Section 9.6, and Table 6, and the exact time of each analysis will depend on actual number of events occurred.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma or serum concentration-time curve
BGB-A317	tislelizumab
CI	confidence interval
CK	creatine kinase
CK-MB	creatine kinase cardiac muscle isoenzyme
CL	clearance
CR	complete response
CT	computed tomography
CPI	checkpoint inhibitor
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-LC13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer-13
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G (eg, IgG1, IgG2, IgG3, IgG4); other types of immunoglobulins include IgD and IgM
irAE	immune-related adverse event

Abbreviation	Definition
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat
IV	intravenous(ly)
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
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
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SOC	system organ class
$t_{1/2}$	half-life
TC	tumor cells
TEAE	treatment-emergent adverse event
TPS	tumor proportion score
TTR	time to response
ULN	upper limit of normal

1 INTRODUCTION

1.1 Background Information on Non-Small Cell Lung Cancer

Lung cancer is the most common cancer worldwide with approximately 1.8 million new diagnoses and 1.59 million deaths worldwide in 2012, which corresponds to the highest incidence among cancers and most common cancer-related mortality (Ferlay et al, 2015). Globally, across all cancer types, lung cancer is more common in men (16.8%) compared to women (8.8%). In China, there were an estimated 733,300 new cases of lung cancer in 2015. Lung cancer is the leading cause of cancer-related death in both men and women with an estimated 610,200 deaths in China in 2015 (Chen et al 2016).

Non-small cell lung cancer (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). Small cell lung cancer (SCLC) accounts 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 seventh edition of tumor, node, metastasis (TNM) Classification of Malignant Tumors (Goldstraw et al 2007). If 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 advanced NSCLC, 5-year survival rates are approximately 36% for Stage IIIA, 26% for Stage IIIB, 10% for Stage IVA, and 1% for Stage IVB (American Cancer Society 2017).

Management of patients with advanced NSCLC is individualized based on molecular and histologic features of the tumor and is discussed as below.

1.2 Current First-Line Treatment of NSCLC

1.2.1 First-Line Treatment for Advanced NSCLC With an *EGFR* Mutation or *ALK* Rearrangement

Genotype-directed therapy has the potential to dramatically improve the balance of benefit and toxicity for selected patients with NSCLC characterized by alterations of driver oncogenes, including sensitizing *EGFR* mutations and *ALK* rearrangements. However, these mutations are more prevalent in adenocarcinoma NSCLC and are very rare in squamous NSCLC (Gou et al 2014). Randomized Phase 3 studies of gefitinib (IPASS), erlotinib (EURTAC), and afatinib (LUX-Lung 3) showed significant improvement of progression-free survival (PFS) and overall response rate (ORR) compared with platinum doublet chemotherapy (Fukuoka et al 2011; Rosell et al 2012; Sequist et al 2013). Similarly, the *ALK* inhibitors crizotinib, ceritinib, and alectinib have demonstrated efficacy in patients with NSCLC that is positive for *ALK* rearrangement as defined by fluorescence in situ hybridization (XALKORI prescribing information; ZYKADIA

prescribing information; ALECENSA prescribing information). Both *EGFR* tyrosine kinase inhibitors (TKIs) and *ALK* inhibitors have been shown to be generally well tolerated.

1.2.2 First-Line Treatment for Advanced NSCLC Without an *EGFR* Mutation or *ALK* Rearrangement

For first-line treatment of advanced NSCLC not harboring identified drug-sensitive gene dysregulation, 2-drug or doublet chemotherapy regimens are recommended (National Comprehensive Cancer Network 2017). No advantage has been noted with addition of a third cytotoxic drug. Platinum-containing doublet chemotherapy remains the standard of care for the most patients with advanced NSCLC (Fennell et al 2016). 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 2017). However, some differences in adverse event profile were noted so that the authors recommend factoring those into decisions regarding which is more appropriate for a given patient.

For patients with non-squamous NSCLC that does not have a sensitizing mutation in epidermal growth factor (EGFR) or an anaplastic lymphoma kinase (ALK) fusion oncogene, standard first-line therapy includes a chemotherapy doublet of cisplatin and pemetrexed, which has been shown to result in superior efficacy and reduced toxicity compared to cisplatin and gemcitabine (NCCN 2017; Scagliotti et al 2008). Median survival time in this study was 11.8 months for pemetrexed plus cisplatin in non-squamous NSCLC compared to 10.4 months for gemcitabine plus cisplatin (HR=0.81; 95% CI, 0.70 to 0.94; p=0.005).

Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF) (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 2017) recommend bevacizumab/chemotherapy for only 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 by the NCCN guideline and the Chinese guideline for patients with non-squamous NSCLC who are lacking identified gene dysregulation, and bevacizumab/chemotherapy is an additional treatment option for this population.

1.2.3 Platinum-Based Regimen for First-Line NSCLC

Several meta-analyses have compared the use of cisplatin and carboplatin as treatments for NSCLC. In general, although the ORR was higher in patients treated with cisplatin than in those treated with carboplatin, the 1-year and OS rates were comparable. When given in combination with a third-generation chemotherapy, cisplatin may result in longer survival than carboplatin (Hotta et al 2004; Ardizzoni et al 2007); but overall benefit was quite marginal, and subgroup analyses including additional, more recent studies indicate that there may be no difference between the 2 agents (Jiang et al 2007; Azzoli et al 2009).

As to safety, cisplatin-based chemotherapy has been associated with more severe nausea and vomiting and nephrotoxicity, while severe thrombocytopenia has been more frequent during carboplatin-based chemotherapy (Hotta et al 2004; Ardizzoni et al 2007). The risk of treatment-related deaths was greater in the cisplatin arm, but this increase was not statistically significant (Jiang et al 2007).

Currently, the standard of care for newly diagnosed, advanced-stage non-squamous NSCLC is a platinum doublet with either cisplatin or carboplatin and a taxane or pemetrexed, with or without bevacizumab. In particular, the combination of a platinum doublet with pemetrexed has been used more widely because of a better tolerability and safety profile (see Section 1.2.4.1).

1.2.4 Pemetrexed-Based Regimen for First-Line NSCLC

Pemetrexed disodium is a novel pyrrolo[2,3-d]pyrimidine-based folic acid analogue. In in vitro studies, pemetrexed inhibited multiple folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl-transferase) crucial in the de novo biosynthesis of thymidine and purine nucleotides (Shih et al 1997).

1.2.4.1 Pemetrexed Plus Platinum Compounds in First-Line NSCLC

Two Phase 2 studies demonstrated that the combination of pemetrexed and carboplatin is tolerable and that its activity in first-line treatment of advanced-stage NSCLC is comparable with other standard platinum doublets commonly used in clinical practice (Kelly et al 2001; Scagliotti et al 2002; Fossella et al 2003; Reck et al 2010). The toxicity profile of the pemetrexed/carboplatin combination appears to be more favorable than that seen with other standard regimens in first-line NSCLC.

A Phase 3 non-inferiority study was conducted comparing the efficacy of cisplatin/pemetrexed (n=862) versus cisplatin/gemcitabine (n=863) in patients with incurable Stage IIIB or IV NSCLC who had received no prior chemotherapy. Median OS, PFS, and time to progression were comparable between the two treatment groups. However, among patients who had adenocarcinoma or large-cell carcinoma, patients treated with cisplatin/pemetrexed had significantly better median OS than patients treated with cisplatin/gemcitabine (12.6 versus 10.9 months for adenocarcinoma [HR=0.84; 95% CI: 0.71, 0.99; p=0.03]); 10.4 versus 6.7 months for large-cell carcinoma [HR=0.67; 95% CI: 0.48, 0.96; p=0.03]). In addition, cisplatin/pemetrexed was associated with better tolerability and safety and resulted in patients requiring less ongoing supportive care (Scagliotti et al 2008).

As well, a supportive study named PRONOUNCE was designed to assess the efficacy and safety of pemetrexed+carboplatin (Pem+Cb) followed by pemetrexed maintenance versus paclitaxel+carboplatin+bevacizumab followed by bevacizumab maintenance (Pac+Cb+Bev) in patients with advanced non-squamous NSCLC. The median PFS was 4.44 months for Pem+Cb versus 5.49 months for Pac+Cb+Bev (HR=1.06; 95% CI: 0.84, 1.35; p=0.610). The median OS for Pem+Cb was 10.5 months versus 11.7 months for Pac+Cb+Bev (HR=1.07; 95% CI: 0.83, 1.36; p=0.615). The 1- and 2-year survival rates were not significantly different between the

arms and were 43.7% and 18.0% for Pem+Cb and 48.8% and 17.6% for Pac+Cb+Bev. ORR and disease control rate (DCR) were 23.6% and 59.9% for Pem+Cb and 27.4% and 57.0% for Pac+Cb+Bev (p=0.414 and 0.575, respectively) (Zinner et al 2015).

1.2.4.2 Pemetrexed Maintenance Therapy in NSCLC

A Phase 3, randomized, double-blind, placebo-controlled study was conducted that explored the use of pemetrexed as switch maintenance in first-line patients with NSCLC after four cycles of induction therapy using one of six standard platinum doublets (gemcitabine, paclitaxel, or docetaxel with either carboplatin or cisplatin). Patients who achieved a complete response (CR), partial response (PR), or stable disease were then randomized to maintenance therapy with pemetrexed plus best supportive care (BSC) or placebo plus BSC until progression (Ciuleanu et al 2009). A significant improvement in PFS was reported for patients who received pemetrexed maintenance therapy compared with those who received placebo (4.04 versus 1.97 months; unadjusted HR, 0.50; 95% CI: 0.42, 0.61; p<0.00001). In patients with non-squamous histology, the median PFS for patients receiving pemetrexed versus placebo was 4.5 months versus 2.6 months (unadjusted HR, 0.44; 95% CI: 0.36, 0.55; p<0.00001). The median follow-up for OS was 11.2 months for patients in the pemetrexed group and 10.2 months for those receiving placebo. The median OS following induction chemotherapy in the Overall Study Population was 13.4 months with pemetrexed and 10.6 months with placebo (unadjusted HR, 0.798; 95% CI: 0.65, 0.95; p=0.012). In the non-squamous population, the median OS was 15.5 months for pemetrexed-treated patients and 10.3 months for patients on placebo (unadjusted HR, 0.70; 95% CI: 0.56 to 0.88; p=0.002).

A second study also explored the value of pemetrexed in the continuous maintenance setting. In this study, patients who had not received prior treatment for lung cancer received four cycles of pemetrexed+cisplatin. Maintenance therapy was continued if stable disease, a PR, or a CR was documented. Patients were then randomized in a 2:1 fashion to either pemetrexed+BSC or placebo+BSC. The median PFS in patients who received pemetrexed was 4.1 months (range 3.2 to 4.6 months) compared with the median PFS of 2.8 months (range 2.6 to 3.1 months) in patients who received placebo. The HR for PFS as assessed by the investigator was 0.62 (95% CI: 0.49, 0.79; p=0.00006). The PFS benefit was internally consistent, and benefit was seen across all clinically important subgroups. OS data from this study are pending (Paz-Ares et al 2012).

1.2.5 Targeted Therapy for NSCLC

Advances in understanding of the molecular pathogenesis of lung cancer have led to the identification of several specific targets for therapeutic agents. Targeting the epidermal growth factor receptor (*EGFR*) and the anaplastic lymphoma kinase (*ALK*) has played a central role in advancing NSCLC research, treatment, and patient outcome over the last several years. Several small molecule targeted agents have been approved globally for patients with NSCLC harboring certain gene dysregulations.

Such small molecule TKIs including drugs that inhibit *EGFR* (eg, erlotinib, afatinib, gefitinib, or osimertinib) and that target rearranged *ALK* (eg, crizotinib, ceritinib, and alectinib) are especially effective in patients whose tumor harbors sensitizing *EGFR* mutation or an ALK fusion gene. In China, the EGFR mutation rate among adenocarcinoma is around 40% to 65%, which is significantly higher than that in Western countries. And a small number (approximately 5%) of NSCLC express the fusion form of ALK in China, which is similar to that reported in Caucasian Population (Zhou and Zhou 2015).

The ROS1 oncogene encodes an orphan receptor tyrosine kinase related to ALK. Crizotinib was approved for metastatic NSCLC whose tumors are ROS1-positive. Crizotinib monotherapy showed marked antitumor activity with the ORR of 72% in patients with advanced ROS1 rearranged NSCLC in an expansion cohort of the Phase 1 study (Shaw et al 2014). However, so far, no head-to-head clinical trial of crizotinib versus first-line doublet chemotherapy demonstrating superiority is available in this population.

1.2.6 Anti-PD-1/Anti-PD-L1 Therapy for Advanced NSCLC

Immune checkpoint-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 signalling in the T cells when engaged by its ligands. The PD-1 signalling 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 (IFN-α) and interferon-gamma (IFN-γ) 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). These monoclonal antibodies have now been approved for the treatment of several cancers, including bladder, lung, head, and neck squamous-cell carcinomas, as well as melanoma, in the US, Europe, and beyond.

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 program 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) for unresectable or metastatic melanoma, metastatic NSCLC that progresses on or after platinum-based chemotherapy, advanced renal cell carcinoma (RCC) after anti-angiogenic therapy, classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem-cell

transplantation (HSCT) and post-transplantation brentuximab vedotin, and head and neck squamous-cell cancer (HNSCC) with disease progression on or after a platinum-based therapy (Antonia et al 2016; United States FDA 2017a; Motzer et al 2015; Gettinger et al 2015; Weber et al 2015; Hodi et al 2016; Rizvi et al 2015; Hellmann et al 2017).

The Phase 3 CheckMate-057 trial compared nivolumab with docetaxel in 582 pre-treated 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; Brahmer et al 2015). In the Phase 3 CheckMate-017 trial, nivolumab was compared with docetaxel in 272 pre-treated 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 (Borghaei 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 Q3W (every 3 weeks). The primary endpoints were OS and PFS both in the Overall Study 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

prescribing information). In the Phase 3 OAK study, 850 patients were randomized to receive atezolizumab or docetaxel. The OS was significantly longer with atezolizumab than with docetaxel in the ITT and PD-L1 Positive Populations. In the ITT analysis set, 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 was 12.6 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).

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 2017b) 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-naive, 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% versus 27.8%), and treatment-related AEs of any grade were less frequent, as were Grade 3, 4, or 5 treatment-related AEs (26.6% versus 53.3%). Based on these results, the FDA approved pembrolizumab in metastatic NSCLC for first-line treatment of patients whose tumors have high level of PD-L1 expression (Reck et al 2016). 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. The 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 prescribing information). This is based on the positive results of the Phase 2 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 as compared to 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 et al 2016).

Keynote-189 sucessfully demonstrated that the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum-based drug resulted in significantly longer overall survival and progression-free survival than chemotherapy alone in patients with previously untreated metastatic nonsquamous NSCLC without activating *EGFR* mutations or known *ALK* translocation. The estimated rate of overall survival at 12 months was 69.2% (95% CI 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI 42.1 to 56.2) in the placebo combination group (HR 0.49, 95% CI 0.38 to 0.64; P<0.001). Median progression-free survival was 8.8 months (95% CI 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI 4.7 to 5.5) in the placebo-combination group (HR 0.52, 95% CI 0.43 to 0.64; P<0.001) (Gandhi et al 2018).

A Phase 1 multicohort study (CheckMate 012) was conducted to explore the safety and efficacy of nivolumab combined with current standard therapies, including a cohort of first-line advanced NSCLC (Hellmann et al 2016). Patients received nivolumab (intravenously, IV) plus platinum-based doublet chemotherapy concurrently Q3W for 4 cycles followed by nivolumab alone until progression or unacceptable toxicity. Regimens were nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (nonsquamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies). No dose-limiting toxicities occurred during the first 6 weeks of treatment. The safety profile of nivolumab plus platinum-based doublet chemotherapy was consistent with that expected for individual agents. The ORR in the non-squamous NSCLC group (n=40) was 43%, median PFS was 6.00 months, PFS rate at 24 weeks was 53% and median OS was 21.5 months. Responses were independent of tumor PD-L1 expression at baseline (Rizvi et al 2016).

A Phase 3 randomized, open-label study (IMpower 150) evaluating the safety and efficacy of atezolizumab in combination with chemotherapy with or without bevacizumab in first-line advanced NSCLC (Reck et al 2017) met its co-primary endpoint of PFS and demonstrated that the combination of atezolizumab and bevacizumab plus chemotherapy (paclitaxel and carboplatin) provided a statistically significant and clinically meaningful reduction in the risk of

disease worsening or death (PFS) compared to bevacizumab plus chemotherapy in the first-line treatment of patients with advanced NSCLC (HR: 0.617, 95% CI: 0.517 to 0.737, $p < 0.0001$), in all populations. Atezolizumab in combination with chemotherapy ± bevacizumab appears to be well tolerated and its safety profile is consistent with known safety risks.

The recent development of checkpoint inhibitors (CPIs) as monotherapy, and in combination with other immunotherapeutic agents or chemotherapeutic agents, provides a new approach for patients with NSCLC, with similar efficacy and safety observed among various CPIs. However, there is still a critical need for predictive biomarkers to identify patients who would receive optimal benefit from the treatment of CPIs. In general, PD-L1 expression has been associated with higher ORRs (range, 23% to 83%) to PD-1/PD-L1 inhibitors (Borghaei et al 2015; Garon et al 2015; Herbst et al 2014; Antonia et al 2014), but responses have also been observed among PD-L1-negative patients (ORRs, 9%–20%) (Garon et al 2015; Herbst et al 2014; Antonia et al 2014; Garon et al 2014). Each PD-1/PD-L1 inhibitor in clinical development has used different anti-PD-L1 antibodies, different scoring cut-offs, and various scoring algorithms (Kerr et al 2015). Therefore, it remains to be explored if PD-L1 expression status is a predictive biomarker for patient selection.

1.3 Unmet Medical Needs for First-Line NSCLC

Patients without *EGFR* mutation or *ALK* rearrangement constitute > 50% of all NSCLC patients in China (Gou et al 2014). Platinum-based chemotherapy doublets with or without bevacizumab are the current standard of care. Platinum doublets are generally associated with a median PFS of 4 to 6 months, and median OS of 8 to 10 months (Kelly et al 2001; Sandler et al 2006; Scagliotti et al 2002; Scagliotti et al 2008; Schiller et al 2002; NCCN 2017). With the introduction of pemetrexed maintenance therapy for non-squamous histology, improvement of PFS (4.1 months vs 2.8 months) and OS (13.9 months vs 11 months), respectively, compared to control arm (placebo) has been observed (Patel et al 2013; Paz-Ares et al 2013). However, despite observed improvements, the overall prognosis remains poor. Therefore, novel therapies are urgently needed for patients with non-squamous NSCLC without *EGFR* mutation or *ALK* rearrangement.

The approval of pembrolizumab monotherapy in NSCLC patients with high PD-L1 expression (tumor proportion scrore ≥ 50%) as first-line treatment and pembrolizumab combined with platinum-based chemotherapy in first-line treatment based on clinically meaningful improvements in OS and ORR compared to standard of care have presented the potential to address the unmet medical needs of patients with NSCLC without *EGFR* or *ALK* alteration (Reck et al 2016). However, there is lack of clinical evidence of anti-PD-1/anti-PDL-l benefit as front-line therapy for Chinese NSCLC patients.

1.4 Background Information on Tislelizumab

1.4.1 Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against programmed cell death protein-1 (PD-1) under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [KD]=0.15 nM). It competitively blocks binding efforts by both programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signalling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and pre-activated, primary peripheral blood mononuclear cells. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to gamma fragment crystallizable region (Fc) receptor IIIA (FcγRIIIA) and complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no antibody-dependent cellullar cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009).

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 toxicokinetics (TK) 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 BGB-A317-304.

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 pharmacokinetics (PK) analysis (data cutoff date 28 August 2017) was conducted using noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, and 2.0 mg/kg, 5.0 mg/kg, and 200 mg Q3W (Phase 1a Parts 1, 2, and 3, and Phase 1b in BGB-A317_Study_001), and patients who received doses of 200 mg Q3W 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 Q3W (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 of 0.173 L/day, volume of distribution (V_d) in the central and peripheral compartments of 2.89 L and 1.76 L, respectively, and half-life ($t_{1/2}$) of 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 Prior Clinical Experience of Tislelizumab

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

Please refer to the tislelizumab 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 (MTD), if any, a recommended Phase 2 dose (RP2D) 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 Q3W; and 200 mg Q3W. In Phase 1b, 323 patients had received tislelizumab in Phase 1b across 9 indication-expansion cohorts.

Overall, for the 439 patients in the study, the median age was 60.0 years, 53.8% of the population was male, and 65.6% of patients were white. The median number of prior anticancer therapy regimens was 2 (range: 0 to 12). The median treatment exposure duration was 2.50 months (range: 0 to 23.0), and the median study follow-up duration was 5.56 months (range: 0.0 to 26.9). As of 28 August 2017, there were 210 patients (47.8%) remaining on study in Study BGB-A317_Study_001.

Preliminary Safety

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

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 anticancer therapy regimens was 2 (range: 0 to 9). The median treatment exposure duration was 1.78 months (range: 0 to 8.0), and the median study follow-up duration was also 1.78 months (range: 0.0 to 8.0). As of 28 August 2017, there were 113 patients (91.9%) remaining on study in Study BGB-A317-102.

Preliminary Safety

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

AST increased (3 patients, 2.4%) and ALT increased (2 patients, 1.6%). All other events occurred in single patients, including a case of retinal detachment (Grade 4).

Preliminary efficacy data are not yet available.

1.4.4.3 BGB-A317-206

This Phase 2 study was conducted to investigate the preliminary antitumor activity, safety, and pharmacokinetics of tislelizumab in combination with chemotherapy as first-line treatment in Chinese patients with locally advanced or metastatic lung Cancer.

As of 21 Feb 2018, a total of 48 patients were treated with tislelizumab, in combination with platinum-based chemotherapy for up to 6 cycles. Sixteen patients with non-squamous NSCLC received pemetrexed + cisplatin, 21 patients with squamous NSCLC received either paclitaxel + cisplatin/carboplatin (cohort A, n = 15) or gemcitabine + cisplatin/carboplatin (cohort B, n = 6), and 11 patients with SCLC received etoposide + cisplatin/carboplatin.

Patients received a median of 3 cycles of tislelizumab (range: 1-7 cycles). As of the data cutoff, 44 patients (92%) remained active on study (range: 1- 155 days), and 4 patients had discontinued study treatment.

Overall, 96% of patients in Study BGB-A317-206 experienced a TEAE, all were reported to be related to chemotherapy and in 42% also related to tislelizumab, and 27% of those were assessed to be immune-related. The most commonly occurring TEAEs occurring in at least 10% of patients were anemia (29 patients, 60.4%) , neutropenia (26 patients, 56.5%) , white blood cell count decrease (25 patients, 52.1%), platelet count decrease (17 patients, 36.9%), decreased appetite (14 patients, 29.2%), nausea (12 patients, 25%), AST increased (11 patients, 22.9%), ALT increased (11 patients, 22.9%), asthenia (11 patients, 22.9%), alopecia (11 patients, 22.9%), pyrexia (9 patients, 18.8%), constipation (8 patients, 16.7%), vomiting (6 patients, 12.5%), hypoesthesia (6 patients, 12.5%), hyponatremia (5 patients, 10.4%), rash (5 patients, 10.4%), pain in extremity (5 patients, 10.4%).

≥ Grade 3 drug-related TEAEs were reported in 23 patients (48%), most of those were indicative of myelosuppression, including decreased counts of neutrophils (10, 20.8%), WBC (5, 10.4%), platelets (3, 6.3%), anemia (6, 12.5%), bone marrow failure (4, 8.3%), thrombocytopenia (2, 4.2%), hyponatremia (3, 6.3%) and ALT increase (2 patients, 4.2%). Serious TEAEs were reported in 7 patients (15%). Immune-related TEAEs (irTEAEs) attributed to tislelizumab were reported in 13 (27%) patients, the most frequently occurring irTEAEs reported were pyrexia (3 patients, 6.3%) and rash (3 patients, 6.3%). One patient experienced ≥ Grade 3 irTEAEs of myocarditis/myositis with a fatal outcome. With the exception of the single Grade 5 event, other related TEAEs were manageable and reversible by interrupting (15 patients, 30%) or discontinuing (4 patients, 8%) study treatment and by appropriate treatment as clinically indicated.

1.4.4.4 Immune-Related Reactions

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

Acute hepatitis and abnormal liver function have been reported, including 1 patient with fatal hepatitis. Additionally, 3.2% of patients experienced treatment-related abnormal liver function tests, and 1.4% of patients experienced immune-related hepatitis or hyperbilirubinaemia.

Pneumonitis has been reported in 2.1% of patients, including 1 patient with fatal pneumonitis.

Colitis has been reported in approximately 2% of patients treated. Diarrhoea has been reported in 6.6% of patients.

Endocrinopathies have been reported including diabetes mellitus (hyperglycemia and ketoacidosis). In addition, thyroiditis, including thyrotoxicosis and hypothyroidism has been reported. Furthermore, hypophysitis has been reported in < 1% of patients treated.

Other immune-related events (< 1% of patients with tislelizumab monotherapy except where noted): skin reactions (20.5%, including rash and pruritus); arthralgia (2.5%); haemolytic anaemia, nephritis, proteinuria (1.8%); encephalitis, neuropathy, arthritis, pancreatitis, stomatitis, uveitis, and dry eye (1.4%).

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

1.5 Study Rationales

1.5.1 Rationale for the Chemotherapy Regimens Administered With Tislelizumab in the Treatment of Advanced Non-Squamous NSCLC

Currently, the standard first-line therapy for patients with advanced NSCLC without targetable genetic aberrations is platinum-doublet chemotherapy (NCCN 2017). With the exception of bevacizumab (Cohen et al 2007), and despite extensive study of multiple targeted and cytotoxic agents, the addition of a third agent to platinum-doublet chemotherapy has not been shown to improve progression-free survival or OS over platinum-doublet chemotherapy alone in randomized studies (NCCN 2017).

Drugs targeting PD-1 and its ligand, PD-L1, have shown a manageable safety profile and robust efficacy including a significant prolongation of OS compared with docetaxel in patients whose disease progressed on platinum-based chemotherapy.

Increasing evidence suggests that the antitumor activity of chemotherapy is mediated not only through cytotoxic effects, but also through immunological effects, including reducing T-regulatory cell activity and enhancing cross-presentation of tumor antigens. Chemotherapy has also been shown to induce PD-L1 expression on tumor cells (Jin and Yoon 2016; Ono Pharmaceutical, 2017; Patel and Kurzrock 2015; Van Der Kraak et al 2016; McDaniel et al 2016;

Gong et al 2011). Combining immunotherapy and chemotherapy could thus additively improve the anticancer activity. The manageable safety profile and the promising antitumor activities observed in other PD-1 antibodies combined with chemotherapy as first-line therapy in patients with advanced NSCLC provide justification for this trial design. Based on preliminary data with tislelizumab monotherapy in a Phase 1 study (BGB-A317_Study_001), tislelizumab appears comparable to other anti-PD-1 CPIs in terms of safety and preliminary activity in patients with advanced solid tumors. In addition, an ongoing Phase 1b study which evaluates the combination of tislelizumab and various standard-of-care (SOC) chemotherapies in first-line NSCLC did not show new safety signals compared to other CPI plus chemotherapy (BeiGene data on file 2017).

This Phase 3 study will assess whether the addition of tislelizumab to SOC chemotherapy will improve the outcome of Chinese patients with metastatic lung cancers, whose disease has a poor prognosis with SOC chemotherapies alone.

1.5.2 Rationale for Selection of Tislelizumab Dose in Combination With Chemotherapy

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 Q3W 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 Q3W 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 Q3W.

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 stable disease (SD), and 6 patients (46%) had a BOR 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 Q3W.

Selection of a Q3W dosing interval is both supported by this preliminary PK evaluation and allows for a convenient integration with common chemotherapeutic regimens.

The doses of all chemotherapy drugs are based on product labelling, literature, and local guidelines. Several Phase 1 and Phase 2 studies showed that the safety profile of anti-PD-1 antibodies in combination with platinum-based doublet chemotherapy was consistent with that expected in individual agents. There were no known overlapping, significant toxicities or

drug-drug interactions between anti-PD-1 antibodies and platinum or pemetrexed observed in these studies.

In conclusion, tislelizumab 200 mg Q3W is the recommended dose for this Phase 3 global safety study.

1.5.3 Rationale for Platinum Doublet Chemotherapy as the Comparator

As described in Section 1.2.4, patients with non-squamous NSCLC that do not have a sensitizing mutation in *EGFR* or an *ALK* fusion oncogene typically receive a standard first-line therapy that 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 (Ciuleanu et al 2009).

1.5.4 Rationale for Primary Endpoint of PFS as Assessed by the IRC

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; in addition, its determination is not generally confounded by subsequent therapies. Meta-analyses have indicated that PFS can be considered a good measure of clinical benefit for patients with locally advanced and/or metastatic NSCLC (Laporte et al 2013).

Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit-risk of the new treatment compared with available therapies (FDA 2007; European Medicines Agency 2012).

New treatment modalities, such as targeted therapies and immunotherapy as monotherapy in patients with highly expressing PD-L1 tumors or in combination with chemotherapy, are emerging as highly effective regimens that are providing improvements in patient outcomes far beyond what has been achieved before (Ellis et al 2014; Langer et al 2016). In particular, immunotherapy has been correlated or associated with durable responses, significant prolongation of PFS, and improvement of quality of life.

The subjectivity in the measurement of PFS assessments is acknowledged—with the fact that the assessment depends on frequency, accuracy, reproducibility, and completeness—and may affect the observed magnitude of effect and carry the risk of bias. Therefore, tumor assessment by the Independent Review Committee (IRC) per RECIST v1.1, scheduled every 6 weeks for the first 52 weeks, regardless of treatment delay until disease progression is to be implemented in this study to ensure lack of bias between the 2 arms.

1.5.5 Rationale for Requiring PD-L1 Testing

The recent development of CPIs, as monotherapy and in combination with other immunotherapeutic agents or chemotherapeutic agents, provides a new approach for patients with NSCLC, with similar efficacy and safety observed among various CPIs. However, there is still a critical need for predictive biomarkers to identify patients who would receive optimal benefit from the treatment of CPIs. In general, PD-L1 protein expression has been associated with higher ORRs (range, 23% to 83%) to PD-1/PD-L1 inhibitors (Borghaei et al 2015; Garon et

al 2015; Herbst et al 2014; Antonia et al 2014), but responses have also been observed among PD-L1-negative patients (ORRs, 9%–20%) (Garon et al 2015; Herbst et al 2014; Antonia et al 2014; Garon et al 2014). Each PD-1/PD-L1 inhibitor in clinical development has used different anti-PD-L1 antibodies, different scoring cut-offs, and various scoring algorithms (Kerr et al 2015). Therefore, it remains to be explored whether PD-L1 expression status is a predictive biomarker for patient selection.

PD-L1 expression (three levels: < 1% TC versus 1%–49% TC versus ≥ 50% TC) is one of the stratification factors. PD-L1 expression as a predictive marker in immunotherapy has been investigated in previous NSCLC trials (Section 1.2.6).

1.5.6 Rationale for Allowing Crossover to Tislelizumab

Despite recent improvements in treatments, the prognosis for patients with advanced NSCLC remains dismal, with median OS of approximately 12.5 months (Sandler et al 2006). Patients who receive second-line treatment for their disease have an even more limited prognosis, with median survival duration of only 9 months in patients with a good performance status (Stinchcombe and Socinski 2008). Formerly approved therapies are associated with significant toxicities (eg, neuropathy, febrile neutropenia, myelosuppression, and alopecia) that negatively impact quality of life.

Anti-PD-1/PD-L1 monoclonal antibodies (mAbs) have shown superior efficacy to docetaxel by increasing the OS by about 2 to 3 months in advanced NSCLC patients who have disease progression during or after a platinum-containing regimen. However, there are no anti-PD-1/PD-L1 mAbs currently approved in China. Hence, patients randomized to the control arm have, at the time of IRC-confirmed tumor progression, the option to cross over to receive tislelizumab as second-line treatment and may potentially gain benefit from the treatment.

1.5.7 Rationale for Allowing Patients to Continue Tislelizumab Containing Treatment Until Loss of Clinical Benefit

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (determined by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Because of the potential for pseudoprogression secondary to tumor-immune infiltration, this study will allow patients randomized to the tislelizumab in combination with chemotherapy treatment arm to remain on tislelizumab-containing treatment, and those patients who cross over from the control arm (chemotherapy only) to receive tislelizumab monotherapy after apparent radiographic progression, provided the benefit-risk ratio is judged to be favorable. Patients should be discontinued for unacceptable toxicity or symptomatic deterioration attributed to disease progression as determined by the investigator after an integrated assessment of radiographic data and clinical status (Section 7.4).

1.5.8 Rationale for Patient-Reported Outcome Assessments

Patient-reported outcome (PROs) assessments have been shown to provide the most robust descriptions of the treatment experience, with the incorporation of multiple modes of endpoint

measurements in clinical trials, and would supplement the data derived from clinical reported CTCAE (Dajczman et al 2008). With growing recognition of the importance of patient-centered care, PROs have also been reported to have positive effects on the well-being of patients with cancer (Basch et al 2016). Evidence of benefits of incorporating PROs in the chemotherapeutic setting, specifically in patients with lung cancer, would further characterize clinical benefit beyond radiographic measures.

The PRO instruments to be used in this study are the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTCT QLC-LC13.

1.6 Benefit-Risk Assessment

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

According to the latest data collected from the Phase 1 study of BGB-A317_Study_001, tislelizumab has demonstrated a favorable safety profile that is consistent with the safety profile of other anti-PD-1 antibodies. In addition, antitumor activity with tislelizumab monotherapy has been observed in a range of tumor types.

As of current Investigator's Brochure (IB) with data cut-off of 28 August 2017, > 400 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3 or 4 irAEs have been observed, and they have been generally reversible and manageable with study drug interruption and/or steroid treatment. (For further information on the safety profile of tislelizumab, please refer to the Investigator's Brochure.) Therefore, the clinical development of tislelizumab, an anti-PD-1 antibody, in combination with chemotherapy, may improve upon outcomes for Chinese patients with advanced solid tumors, including NSCLC.

The present study is a randomized study designed to compare the safety and efficacy of tislelizumab combined with chemotherapy in patients with advanced non-squamous NSCLC with wild-type *EGFR*. The benefit/risk assessment based on available tislelizumab Phase 1 data and the publications from Phase 3 studies of other anti-PD-1 antibodies is considered positive; the study design, which randomizes patients to tislelizumab combined with chemotherapy compared with chemotherapy alone at 2:1 ratio, is considered justified from a benefit/risk perspective.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To compare the progression-free survival (PFS) as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in an Intent-To-Treat (ITT) analysis set between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in chemotherapy-naive patients with Stage IIIB or Stage IV (as classified according to American Joint Committee Cancer 7th Edition of Cancer Staging Manual) non-squamous, non-small cell lung cancer (NSCLC).

2.1.2 Secondary Objectives

- To compare overall response rate (ORR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To compare duration of response (DOR) as assessed by the IRC and by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To compare overall survival (OS) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in an ITT analysis set.
- To compare PFS as assessed by the investigator per RECIST v1.1 between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone in an ITT analysis set.
- To compare health-related quality of life (HRQoL) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone.
- To evaluate the safety and tolerability of tislelizumab combined with platinum-pemetrexed compared with platinum-pemetrexed alone.
- To evaluate the correlation between programmed death-ligand1 (PD-L1) expression levels by immunohistochemistry (IHC) and antitumor activity of tislelizumab combined with platinum-pemetrexed.

2.1.3 Exploratory Objectives

- To compare tumor assessment outcomes (eg, DCR, TTR) between tislelizumab combined with platinum-pemetrexed and platinum-pemetrexed alone as assessed by the investigator per RECIST v1.1.
- To assess tumor and blood biomarkers of tislelizumab response, resistance, and patient prognosis.
- To characterize the pharmacokinetics of tislelizumab when given in combination with platinum-pemetrexed.
- To assess host immunogenicity to tislelizumab.

2.2 Study Endpoints

2.2.1 Primary Endpoint

- PFS as assessed by the IRC–the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the IRC per RECIST v1.1 in an ITT analysis set.

2.2.2 Secondary Endpoints

- ORR as assessed by the IRC–the proportion of patients who had complete response (CR) or partial response (PR) as assessed by the IRC per RECIST v1.1 in ITT analysis set.
- DOR as assessed by the IRC–the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as assessed by the IRC per RECIST v1.1 in ITT analysis set with documented objective responses.
- OS–the time from the date of randomization to the date of death due to any cause in an ITT analysis set.
- PFS as assessed by the investigator–the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined by the investigator per RECIST v1.1 in an ITT analysis set.
- Overall response rate (ORR) as assessed by the investigator–the proportion of patients who had CR or PR as determined by the investigator per RECIST v1.1 in ITT analysis set.
- Duration of response (DOR) as assessed by the investigator–the time from the first occurrence of a documented objective response to the time of relapse, or death from any cause, whichever comes first, as determined by the investigator per RECIST v1.1 in ITT analysis set with documented objective responses.
- HRQoL–measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Lung Cancer (EORTC QLQ LC13) and Core 30 (EORTC QLQ-C30) as presented in patient-reported outcomes
- Incidence and severity of treatment-emergent AEs (TEAEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0.
- PD-L1 expression by IHC as a predictive biomarker for response.

2.2.3 Exploratory Endpoints

- DCR–the proportion of patients who had a CR, partial response (PR), or stable disease (SD) as assessed by the investigator per RECIST v1.1.
- TTR–the time from randomization to the first occurrence of a documented objective response as assessed by the investigator per RECIST v1.1.
- Status of exploratory biomarkers, including but not limited to: PD-L1, tumor mutation burden (TMB), and immune-related gene expression profiling (GEP) in archival and/or freshly obtained tumor tissues and blood (or blood derivatives) obtained before, during, or

after treatment with tislelizumab or at progression and the association with disease status and/or response to tislelizumab in combination with chemotherapy.

- Summary of serum concentrations of tislelizumab.
- Assessments of immunogenicity of tislelizumab by determining the incidence of antidrug antibodies (ADAs).

3 STUDY DESIGN

3.1 Summary of Study Design

This is an open-label, randomized, multicenter Phase 3 study designed to compare the efficacy and safety of tislelizumab combined with cisplatin or carboplatin + pemetrexed (Arm A) and cisplatin or carboplatin + pemetrexed alone (Arm B) as first-line treatment in approximately 320 patients who have Stage IIIB or IV non-squamous NSCLC, whereby choice of platinum (cisplatin or carboplatin) will be at the investigator's discretion.

The primary endpoint of the study is measured by PFS as assessed by the IRC in the ITT analysis set.

Patients who have not received chemotherapy with histologically confirmed non-squamous, locally advanced, or metastatic NSCLC (Stage IIIB or IV) are eligible. Histology of non-squamous NSCLC will be confirmed at the investigator's site. Patients with known *EGFR* mutation or *ALK* rearrangement are ineligible for the study; for patients without documented tissue-based documentation of EGFR status, fresh or archival tumor tissues are required for *EGFR* mutation assessment. Archival tumor specimens will be prospectively tested for PD-L1 expression by a central laboratory. If archived formalin-fixed paraffin-embedded (FFPE) tissue is not sufficient for PD-L1 analysis, a fresh biopsy sample will be needed. PD-L1 status will be characterized as PD-L1 membrane staining on tumor cells (TC) via the Ventana SP263 assay.

Patients will be stratified by disease stage (IIIB versus IV), and PD-L1 expression (three levels: < 1% TC versus 1%–49% TC versus ≥ 50% TC). Patients whose tissues are unevaluable for PD-L1 expression (please refer to Section 7.8 for detailed information) will be included in the < 1% TC group. All patients will be randomized by a 2:1 ratio to receive one of the following treatment regimens:

Induction phase (4 to 6 cycles, Q3W):

Arm A: tislelizumab + carboplatin or cisplatin + pemetrexed

Arm B: carboplatin or cisplatin + pemetrexed

Maintenance phase (Q3W):

Arm A: tislelizumab + pemetrexed

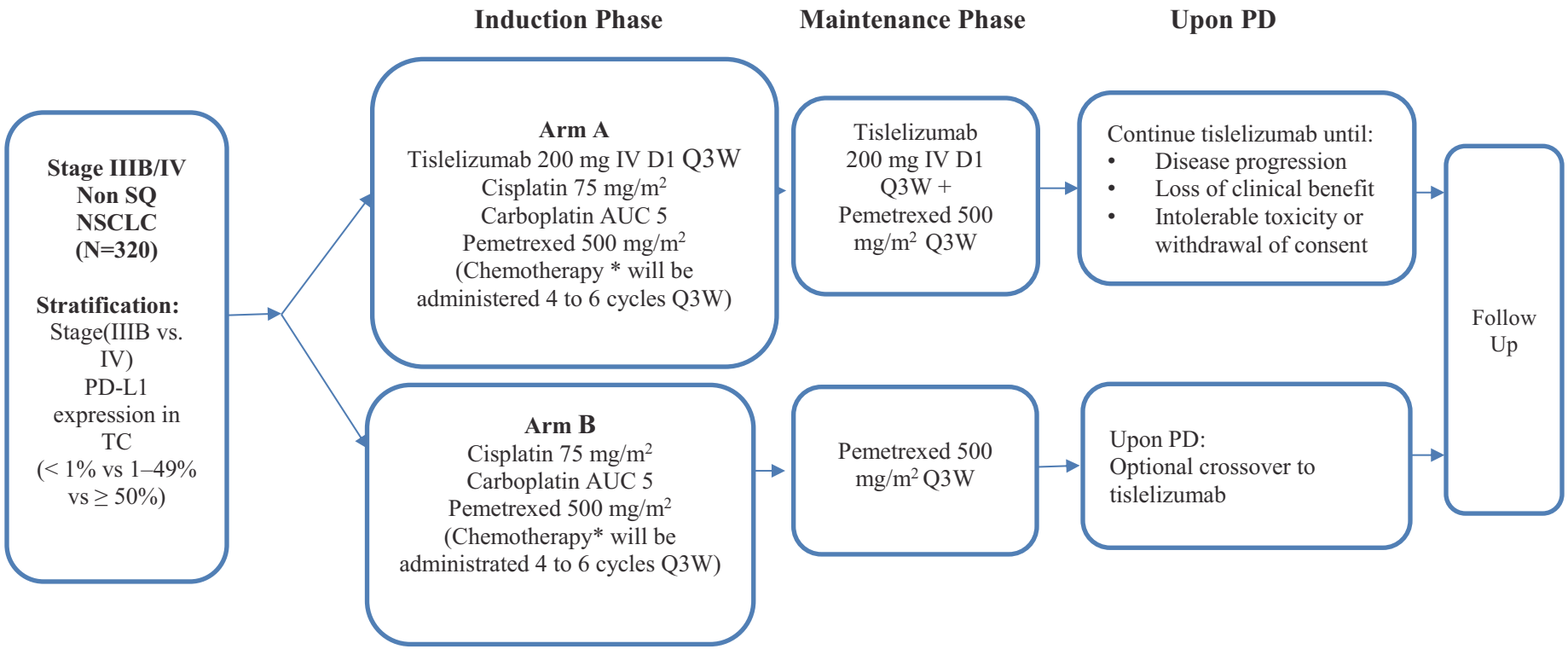
Arm B: pemetrexed

The following is the study schematics:

Phase 3 Study Schema for tislelizumab plus Chemotherapy versus Chemotherapy alone as First-Line Therapy for NSCLC

The study design schematics is presented in Figure 1.

Figure 1. Study Schema



*Chemotherapy: Cisplatin or Carboplatin + Pemetrexed

Abbreviations: IV, intravenous; PD, progressive disease; PD-L1, programmed death-ligand 1; NSCLC, non-small cell lung cancer; TC, tumor cells; Q3W, every 3 weeks

Cisplatin 75 mg/m^2 administered as an IV infusion over 2 hours Q3W for 4–6 cycles

Carboplatin AUC 5 administrated as an IV infusion over 15 minutes Q3W for 4–6 cycles

Pemetrexed 500 mg/m^2 administered as an IV infusion over 10 minutes Q3W

For all study procedures, see Section 7 and Appendix 1.

3.2 Screening Period

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Archival tumor tissue must be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is required (Section 7.8).

3.3 Treatment Period

After completing all screening activities, eligible patients will be randomized. The selection of platinum will be determined by the investigator and documented prior to randomization. The number of cycles of induction treatment (4 to 6) will be at the discretion of the investigator. Induction treatment will be administered on a Q3W schedule whereby Q3W constitutes one cycle until one of the following occurs (whichever occurs first): 1) completed administration of 4 to 6 cycles; 2) unacceptable toxicity; or 3) documented disease progression per RECIST v1.1.

After the induction phase, patients randomized into either Arm A or B will continue treatment with pemetrexed maintenance therapy until progressive disease, unacceptable toxicity, or death, whichever occurs first.

For all patients in Arm A, if progression of disease is unconfirmed and the patient is clinically stable, it is at the discretion of the investigator to continue the assigned study treatment per protocol until disease progression is confirmed at least 28 days (or at the next scheduled tumor assessment) from the date of the scan suggesting disease progression. If a patient has confirmed disease progression per RECIST v1.1, the patient should not receive further chemotherapy treatment on study, and should follow the following guidance:

For Arm A (Experimental arm):

Patients who experience progressive disease per RECIST v1.1 during chemotherapy combination phase (induction or maintenance phase) or thereafter while receiving tislelizumab monotherapy will be permitted to continue tislelizumab monotherapy provided they meet all the following additional criteria:

1. Evidence of clinical benefit as assessed by the investigator
2. Absence of symptoms and signs (including clinically significant worsening of laboratory values [eg, new or worsening hypercalcemia]) indicating unequivocal progression of disease
3. No decline in ECOG performance status that can be attributed to disease progression
4. Absence of tumor progression at critical anatomical sites (eg, CNS disease) that cannot be managed by protocol-allowed medical interventions

5. Patients must provide written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial progression

For Arm B (Control arm):

Patients randomized to Arm B who develop radiographic disease progression per RECIST v1.1 (to be confirmed by the IRC) will be given the option to cross over (see Section 7.4) to receive tislelizumab monotherapy if they meet all the following criteria:

1. ECOG PS of ≤ 1
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, central nervous system [CNS] disease) that cannot be managed by protocol-allowed medical interventions
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen

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.

Crossover is optional and is at the discretion of the investigator and with the sponsor's agreement.

For Arm A and Arm B:

Once patients are receiving tislelizumab monotherapy, the investigator may consider continuing tislelizumab monotherapy beyond investigator-assessed progression, provided that patients meet the above outlined criteria, and upon discussion with the medical monitor.

The decision to continue tislelizumab beyond investigator-assessed progression must be documented in the study records.

Patients may continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study completion by the sponsor, start of a new anticancer therapy, or death, whichever occurs first.

Patients will undergo tumor assessments at baseline and every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remaining 6 months of Year 1, and after completion of the Week 52 tumor assessment, tumor assessment will continue every 12 weeks (± 7 days) based on RECIST v1.1, regardless of dose delays to manage toxicities. Patients will undergo tumor assessments until radiographic disease progression per RECIST v1.1, loss of clinical benefit (for tislelizumab-only patients who continue treatment after radiographic disease progression according to RECIST v1.1), withdrawal of consent, study completion by sponsor, start of a new anticancer therapy, or death, whichever occurs first.

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

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]

v5.0), and laboratory results. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.5 and the Schedule of Assessments (Appendix 1).

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

The EOT 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 continue tumor assessments as outlined in Section 7.6.

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 study drug (including chemotherapy-only) 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 AE or is a new anticancer therapy) at 60 days, and 90 days (±14 days) after the last dose of study drug (including chemotherapy-only), regardless of whether 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 8.6.

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) will continue to undergo tumor assessments according to Section 7.6 and the Schedule of Assessments (Appendix 1), until the patient experiences disease progression, withdraws consent, is lost to follow-up, dies, until the study completes, or the patient starts a new anticancer therapy, whichever occurs first.

After patients are discontinued from study treatment, they are followed via telephone calls, patient medical records, and/or clinic visits for updates on survival and further anticancer therapy (anticancer therapy during Survival Follow-up and the patient's overall response to them will also be collected including the date of disease progression of subsequent anticancer therapy). Clinic visits occur 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 completion by the sponsor.

3.6 Discontinuation From the Study Treatment or From the Study

3.6.1 Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment 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 7.4.1) and survival (Section 3.5), if possible.

The primary reason for discontinuation from the study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue from the study treatment for reasons that include, but are not limited to, the following:

- Radiographic disease progression per RECIST v1.1
- 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 the study treatment
- Use of any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and patent medicines] for the treatment of cancer) (Section 6.2.2)
- 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

The end of study is defined as the timepoint when data collection will stop. The primary analyses will be conducted when the predefined PFS 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 disease progression, is lost to follow-up, or withdraws from study, or until study completion by sponsor.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early 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 investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing Institutional Review Board (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

The sponsor has the right to close a site at any time. The decision will be notified 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 (GCP), 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

Each patient eligible to participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. 18 to 75 years old on the day of signing the ICF
3. Histologically confirmed, locally advanced (Stage IIIB) not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) non-squamous NSCLC

   Patients with tumors of mixed non-small cell histology (squamous and non-squamous) are eligible if the major histological component appears to be non-squamous.
4. Patients must be able to provide fresh or archival tumor tissues (FFPE blocks or approximately 15 [at least 6] freshly cut unstained FFPE slides) with an associated pathological report (non-squamous). Patients must be able to provide documentation of wild-type *EGFR* reported by a tissue-based test. For patients without documented *EGFR* status, archival or fresh tumor tissues are required for *EGFR* mutation assessment prior to

enrollment. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory. PD-L1 expression will be assessed centrally.

5. ECOG performance status ≤ 1
6. Patients must have at least one measurable lesion as defined per RECIST v1.1.
7. Have had no prior systemic chemotherapy for advanced or metastatic NSCLC.

   Patients who have received prior neo-adjuvant, adjuvant chemotherapy, radiotherapy, or chemoradiotherapy with curative intent for non-metastatic disease must have experienced a disease-free interval of at least 6 months from the last dose of chemotherapy and/or radiotherapy prior to randomization.
8. Life expectancy ≥ 12 weeks
9. Patients must have adequate organ function as indicated by the following laboratory values (obtained within 7 days prior to randomization):
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, hemoglobin ≥ 90 g/L. Note: Patients must not have required a blood transfusion or growth factor support ≤ 14 days before sample collection
   - International normalized ratio (INR) or prothrombin time ≤ 1.5 x ULN
   - Activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
   - Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 3 x ULN for patients with Gilberts syndrome)
   - Aspartate and alanine aminotransferase (AST and ALT) ≤ 2.5 x ULN or AST and ALT ≤ 5 x ULN for patients with liver metastases
10. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and 120 days after the last dose of tislelizumab, and have a negative urine or serum pregnancy test ≤ 7 days of randomization.
11. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for 120 days after the last dose of tislelizumab.

4.2 Exclusion Criteria

Patients who meet any of the following criteria must be excluded from this study:

1. Diagnosed with NSCLC that harbors an *EGFR*-sensitizing mutation or *ALK* gene translocation
2. Received any approved systemic anticancer therapy, including hormonal therapy, within 28 days prior to initiation of study treatment
3. Received prior treatment with EGFR inhibitors or ALK inhibitors
4. Received prior therapies targeting PD-1 or PD-L1

5. Treatment with systemic immune-stimulatory agents (including but not limited to interferons, interleukin-2, and tumor necrosis factor) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to randomization (prior treatment with cancer vaccines is allowed)
6. Has received any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of randomization
7. With history of interstitial lung disease, non-infectious pneumonitis, or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc
8. Clinically significant pericardial effusion
9. Clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to randomization
10. Severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc:
    - Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
    - Received therapeutic oral or IV antibiotics within 2 weeks prior to randomzation
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. Any major surgical procedure requiring general anesthesia ≤ 28 days before randomization
13. Unresolved acute effects of prior therapy (eg, adjuvant chemotherapy) > CTCAE Grade 1 at the time of randomization, except for alopecia, that are not likely to constitute safety risk

14. Received > 30 Gy of radiation for lung lesions within 6 months of the first administration of the study treatment
15. Any active malignancy ≤ 2 years before randomization, except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)
16. Known Human Immunodeficiency Virus infection
17. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL (2500 copies/mL) or patients with active hepatitis C virus (HCV) should be excluded. Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA < 500 IU/mL [2500 copies/mL]), and cured hepatitis C patients can be enrolled. The HBV DNA test will be performed only for patients who have a positive antibody to hepatitis B core antigen (anti-HBc antibody) test. The HCV RNA test will be performed only for patients who test positive for HCV antibody.
18. Active autoimmune diseases or history of autoimmune diseases that may relapse

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

    - Controlled Type I diabetes
    - Hypothyroidism (provided it is managed with hormone replacement therapy only)
    - Controlled celiac disease
    - Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
    - Any other disease that is not expected to recur in the absence of external triggering factors
19. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before randomization

    Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

    - Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
    - Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
    - Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

20. Any of the following cardiovascular criteria:

- Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before randomization
- Symptomatic pulmonary embolism ≤ 28 days before randomization
- Any history of acute myocardial infarction ≤ 6 months before randomization
- Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 5) ≤ 6 months before randomization
- Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before randomization
- Any history of cerebrovascular accident ≤ 6 months before randomization
- Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before randomization
- Any episode of syncope or seizure ≤ 28 days before randomization

21. Prior allogeneic stem cell transplantation or organ transplantation
22. Was administered 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.

23. Underlying medical conditions or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or adverse events or result in insufficient compliance during the study according to the investigator's judgment.
24. History of allergic reactions to cisplatin, carboplatin, or pemetrexed

    Patients with hearing impairment or ≥ Grade 2 peripheral neuropathy (as defined by NCI CTCAE v5.0 criteria) will not be eligible for cisplatin chemotherapy.

25. CrCl < 60 mL/min for cisplatin or < 45 mL/min for carboplatin
26. Concurrent participation in another therapeutic clinical study

5 STUDY TREATMENT

5.1 Formulation, Packaging, and Handling

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 of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a

Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The label will include at a minimum: the 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 the 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 and 8^{o}C and protected from light.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding tislelizumab.

5.1.2 Chemotherapy Agents

Management (ie, handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines and/or prescribing information.

For further details, see the manufacturer's prescribing information for the respective chemotherapy agents.

5.2 Dosage, Administration, and Compliance

Dosing schedules for both arms, broken out by individual arm, are provided in Table 1. The first dose of study drug is to be administered within 2 business days of randomization or enrollment. 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.

For each cycle, tislelizumab will be administered before chemotherapy drugs. The order of chemotherapy drug administration will be conducted in accordance with the relevant local guidance and/or clinical practice.

Patients should receive antiemetics and IV hydration for platinum-pemetrexed treatments according to the local standard of care and manufacturer's instruction. Due to their immunomodulatory effects, premedication with steroids should be limited when clinically feasible. In addition, in the event of pemetrexed-related skin rash, topical steroid use is recommended as front-line treatment whenever it is clinically feasible.

In special situations (eg, when the administration is delayed due to management of adverse events or in the case of an infusion-related reaction), administration of the subsequent study drugs might be delayed to the second day of each cycle.

Table 1. 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.
Pemetrexed	500 mg/m^2	Every 3 weeks	Intravenous	See Section 3.3.
Cisplatin	75 mg/m^2	Every 3 weeks	Intravenous	See Section 3.3.
Carboplatin	AUC 5	Every 3 weeks	Intravenous	

5.2.1 Tislelizumab

Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (Q3W).

Tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

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

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 period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (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 Section 8.7 and Appendix 6.

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

5.2.2 Chemotherapy

Carboplatin or cisplatin will be administered after completion of the pemetrexed during the induction phase.

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W until disease progression or unacceptable toxicity. All patients should receive the appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all patients should receive the appropriate corticosteroid pre-medications as per the local approved label. Additional pre-medications should be administered as per standard practice.

Carboplatin AUC 5 will be administered as an IV infusion over 15 minutes Q3W for 4 to 6 cycles immediately after pemetrexed. Additional pre-medications should be administered as per standard practice.

Cisplatin 75 mg/m^2 will be administered as an IV infusion over 2 hours Q3W for 4 to 6 cycles. All patients should receive adequate hydration (including pre-treatment hydration) and diuretics. Urinary output > 2000 mL must be maintained in the following 24 hours of the infusion.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any and all AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of chemotherapy therapy. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

5.3 Overdose

Any overdose (defined as ≥ 600 mg of tislelizumab in a 24-hour period) or incorrect administration of study drug should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via the SAE reporting process as described in Section 8.6. Supportive care measures should be administered as appropriate.

5.4 Investigational Medicinal Product Accountability

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

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

5.5 Dose Delay or Modification

Dose delay is defined as interruption of the tislelizumab regimen (ie, the drug is withheld beyond visit window). Dose interruption is defined as an interruption of infusion.

Every effort should be made to administer the study drug(s) on the same day according to the planned dose and schedule, provided the patient's condition allows. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below.

The tumor assessment schedule will not be altered if chemotherapy or tislelizumab are delayed or discontinued.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays). Patient should continue study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor.

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 General Guidance Regarding Dose Modifications

The severity of adverse events will be graded according to the NCI-CTCAE v5.0 grading system.

- Dose modifications for chemotherapy will be performed per local practice and per prescribing information according to the treating physician's clinical judgment (see Section 5.5.3).
- Tislelizumab might be delayed as defined in Section 5.5.2.
- For any events already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator considers it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that turns to Grade 2 during treatment, this will be considered a shift of 1 grade and treated as Grade 1 toxicity for dose modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to 1 component of the study treatment and the dose of that component is delayed or modified in accordance with the guidelines below, other components may be administered if there is no contraindication.
    - If one component of chemotherapy is discontinued permanently during the 4 to 6 cycles of treatment for reasons other than progressive disease (PD), the other component of chemotherapy may be continued per the guidelines in the study protocol and as per local practice. Tislelizumab may continue as indicated.
    - If both components of the chemotherapy are withheld because of toxicity for > 2 cycles, chemotherapy should be discontinued; tislelizumab may be continued if the toxicity resulting in chemotherapy discontinuation is not considered by the investigator to be related to tilselizumab. Exceptions based on clinical benefit require the prior approval of the medical monitor.
    - If tislelizumab is discontinued permanently during the 4 to 6 cycles of chemotherapy treatment, the patient may continue the chemotherapy.
- Administration of chemotherapy should ideally remain synchronized with pre-defined cycles and tislelizumab infusions (Section 5.2.1, 5.5.2).
    - If chemotherapy related toxicities warrant dose delays, chemotherapy administration should be restarted to ideally coincide with the next treatment cycle or may be given during an unscheduled visit and resynchronized at later cycle, if possible. For example, if chemotherapy related toxicity resolves on Day 7, chemotherapy may be administered that day and resynchronized as permissible at next or subsequent cycle; if chemotherapy

related toxicity resolves on Day 14, chemotherapy may be administered on Day 1 of the next planned cycle.

- Following either completion of or discontinuation from chemotherapy, tislelizumab should be continued as scheduled, if clinically appropriate (Section 3.3). Pemetrexed maintenance after completion of doublet chemotherapy is also permitted.

Dose modification guidelines for chemotherapy, described below (Section 5.5.3), depend on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing the patient's compliance and access to supportive care.

5.5.2 Dose Delay or Modification for Tislelizumab

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

The patients should resume tislelizumab treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) within 12 weeks after last dose of tislelizumab. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment.

If a dose is delayed for tislelizumab for ≤ 10 days for a planned dosing cycle (eg, Cycle 3 Day 1), tislelizumab should be administered (on the same day with chemotherapy, if applicable). If the delay is > 10 days, the patient should skip the tislelizumab dose, and tislelizumab will be administered on Day 1 of the next planned cycle (ie, Cycle 4 Day 1).

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 the sponsor's medical monitor.

Dose modification related to irAEs and infusion-related reactions are described in Appendix 6 and Section 8.7.1, respectively.

5.5.3 Dose Delay or Modifications for Chemotherapy Treatment

Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the investigator's clinical judgment.

Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by > 10% from baseline (or the new reference body weight). Chemotherapy doses should not be modified for any body weight change of < 10%.

Study-drug-related toxicities must be resolved to baseline or Grade 0 and 1 prior to administering the next dose, except for alopecia or Grade 2 fatigue. A maximum of 2 dose reductions for each chemotherapeutic agent except for carboplatin are permitted. Only one dose reduction is permitted for carboplatin. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose escalations in this study. If additional reductions are required, that chemotherapeutic agent must be

discontinued. Chemotherapy treatment may be delayed up to 21 days, if the reason for the delay is toxicity/adverse event. All subsequent chemotherapy doses must be rescheduled according to the last chemotherapy dose administration date.

SELECTED PRECAUTIONS:

- Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively following the local clinical practice and/or the guidelines.
- Renal Toxicity:
    - Nephrotoxicity is common with cisplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
    - Pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min.
- Ototoxicity and sensory neural damage should be assessed prior to each cycle. Cisplatin is contraindicated in patients with a pre-existing hearing deficit.

For toxicities not listed above, dose modifications are permitted per local standards.

Guidance regarding dose modifications for certain toxicities is presented in detail in Appendix 10.

5.6 Criteria for Discontinuing Chemotherapy Regimens

Except where specified above, both chemotherapy drugs in the platinum doublet chemotherapy regimen should be discontinued for any of the following:

- Any Grade 4 peripheral neuropathy.
- Persistent Grade 3 paraesthesia.
- Grade 3 or 4 drug-related thrombocytopenia associated with clinically significant bleeding.
- Any drug-related liver function test abnormality value that meets any of the following criteria requires discontinuation:
    - AST or ALT > 5-10 x ULN for > 2 weeks
    - AST or ALT > 10 x ULN
    - Total bilirubin > 5 x ULN
    - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any cisplatin-related decrease in creatinine clearance to < 30 mL/min (using the Cockroft-Gault formula) requires discontinuation of cisplatin or change to carboplatin.
- Any pemetrexed-related continuous decrease in creatinine clearance to < 45 mL/min (using the Cockroft-Gault formula) requires discontinuation of pemetrexed.
- Any drug-related AE that recurs after 2 prior dose reductions (or 1 prior reduction for carboplatin) for the same drug-related AE requires discontinuation of the drug(s).

- Any Grade 3 or 4 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 AE that the investigator considers related to study drug and inappropriate to be managed by dose reduction(s) requires discontinuation of drug(s). The drug not felt to be related to the event may be continued.
- If any toxicity does not resolve within 21 days, that component will be discontinued.

For toxicities not listed above, the investigator's medical judgment would determine whether chemotherapy regimen should be discontinued, in accordance with patient's well-being and local standards.

Refer to Section 3.4 regarding safety follow-up procedures.

6 PRIOR AND CONCOMITANT THERAPY

6.1 Prior Therapy

The exclusion criteria (Section 4.2) specify that patients will not have received prior systemic therapy with *EGFR* inhibitors or *ALK* inhibitors or therapies targeting PD-1 or PD-L1.

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, antiemetics, antidiarrheals) and in a patient's interest are allowed. Patients should receive full supportive care, including epoetin and other hematopoietic growth factors, transfusions of blood and blood products, antibiotics, antiemetics, and/or other applicable medications, as needed.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (Appendix 6) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

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. Peg-IFN, 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). The investigator might use other antiviral agents, if appropriate, following local guidelines. Management of antiviral therapy is at the discretion of the investigator.

Patients with active hepatitis C should undergo treatment with antiviral therapy following the AASLD guideline or the local guidelines as appropriate. However, interferon-based therapy for either HBV or HCV is not permitted on study. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to enrollment and at a stable dose. Bisphosphonates are permitted during the study for a non-malignant indication.

Whole-brain radiation therapy and stereotactic radiosurgery are permitted for patients with disease progression limited to the CNS. 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 or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the 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:

- 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.
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine] for the treatment of cancer) is not allowed.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.1.
- Live vaccines ≤ 4 weeks before randomization and 60 days following the last dose of study drug(s).
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study.
- Ibuprofen administration should be avoided or restricted in patients with a creatinine clearance between 45 mL/min and 79 mL/min (Section 6.3).
    - If concomitant ibuprofen use cannot be avoided, at a minimum, administration of ibuprofen should be avoided for 2 days before, the day of, and 2 days following

administration of pemetrexed, and monitor patients more frequently for adverse reactions, including myelosuppression, renal, and gastrointestinal toxicity (Pemetrexed prescribing information).

6.2.3 Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Patients should avoid alcohol completely and should avoid other addictive drugs during the study.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.

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.

6.3 Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between the study drugs (tislelizumab) and small molecule drug products is very low, given that tislelizumab is a therapeutic monoclonal antibody. Because tislelizumab is expected to be degraded into amino acids and recycled into other proteins, it is unlikely to influence drug metabolizing enzymes or transporters.

Ibuprofen has been shown to increase pemetrexed exposure and poses a risk in patients with mild/moderate renal impairment. Hence ibuprofen usage is discouraged in those patients (Section 6.2.2).

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 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. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The screening period begins on the first day screening procedure is conducted. 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 (Appendix 1). 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.

Results of routine assessment performed per standard of care 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.

Only procedures conducted during the screening visit 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 7.5), Tumor and Response Evaluations (Section 7.6), and Biomarkers (Section 7.8).

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

Demographic data will include age or date of birth, gender, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; 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.

Cancer history will include an assessment of prior surgery, prior radiotherapy, and 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 9 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential."

7.1.3 Informed Consent and Screening Log

Voluntary, written, informed consent for participation in the study must be obtained before performing any study-specific procedures. The ICFs 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 to confirm that patients meet all eligibility criteria before randomization. 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, forced expiratory volume in the first second (FEV1) < 60% or diffusing capacity for carbon monoxide (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.

Test 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 or study drug administration.

7.2.2 Patient Numbering

After obtaining informed consent, study site personnel will access the Interactive Response Technology (IRT) system to assign a unique patient number to a potential study participant.

7.2.3 Randomization

Site personnel will access the IRT system to randomize to treatment assignment and to assign study drugs. Study treatment must commence within 2 business days after randomization/treatment assignment.

7.3 Tislelizumab and Chemotherapy Dispensation

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

7.4 Crossover

7.4.1 Crossover for Patients in Chemotherapy in Arm B With Documented and IRC Confirmed Disease Progression

Patients who are randomized into the chemotherapy arm (Arm B) will have the opportunity to crossover to receive tislelizumab once they experience radiographic disease progression on chemotherapy, that is, if disease progression per RECIST v1.1 has been confirmed by the IRC and approval by the medical monitor has been obtained. Patients who permanently discontinue chemotherapy due to an adverse event, withdrawal of consent, or for any reason other than progressive disease will not be eligible for crossover. Crossover patients should not initiate treatment with tislelizumab prior to resolution of treatment-related toxicities to ≤ Grade 1 (NCI-CTCAE v5.0) or baseline, with the exception of select chemotherapy-related toxicities such as hair loss, but should be initiated within 42 days (if applicable), and upon consultation with the medical monitor.

Patients who develop radiographic disease progression per RECIST v1.1 will be allowed to cross over to start tislelizumab provided that there is confirmation of progressive disease as assessed by the IRC and the patients meet all the following criteria:

1. ECOG PS ≤ 1
2. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, CNS disease) that cannot be managed by protocol-allowed medical interventions
3. Patient provided written consent to acknowledge that tislelizumab is an experimental treatment used after failure of prior first-line platinum-containing regimen

Crossover is optional and is at the discretion of the investigator with the sponsor's agreement.

7.4.2 Crossover Assessments and Procedures

If a patient experiences radiographic disease progression per RECIST v1.1 while on chemotherapy (Arm B), the investigator should discuss treatment options with the patient and determine whether there is desire and the patient meets criteria which not only include baseline inclusion and exclusion criteria but also the ones mentioned in Section 7.4.1 to cross over to tislelizumab monotherapy. If that is the case, radiographic imaging scans (most recent at time of progressive disease and, if not already transmitted, at minimum at time of baseline and SLD nadir) need to be submitted to the IRC to obtain an independent assessment and confirmation of progressive disease.

Provided that there is IRC confirmation of progressive disease and the sponsor approves, patients can cross over. Procedures and assessments obtained at the time of assessing progressive disease may be used as appropriate for the start of the crossover phase of the study if those procedures and assessments are performed within 28 days of the first dose of tislelizumab monotherapy in the crossover phase.

The tumor image used to determine progressive disease can be used as the new baseline image for the crossover phase if:

1. it occurred within 28 days prior to receiving the first dose of tislelizumab monotherapy, and
2. no study treatment was administered between the image and the first dose of tislelizumab monotherapy.

Otherwise, a new baseline image must be performed prior to tislelizumab monotherapy treatment.

The safety assessments for patients who cross over to tislelizumab monotherapy should follow the schedule of Arm A Tislelizumab safety assessment procedure. Patients who permanently discontinue the crossover phase will follow the same Safety Follow-up and Survival Follow-up phases.

7.5 Safety Assessments

For all patients, Day 1 visits for each cycle and corresponding study assessments need to occur at the clinical study site.

For all patients, at the investigator's discretion, review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15 (for further details, see Appendix 1).

7.5.1 Vital Signs

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

Height (baseline only) and weight should be measured and recorded in the eCRF.

For the first two infusions of tislelizumab, 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.

7.5.2 Physical Examinations

During the screening visit, a complete physical examination will be conducted including evaluation of 1) head, eyes, ears, nose, throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory, 6) gastrointestinal; and 7) neurological. Any abnormality identified during screening will be graded according to NCI-CTCAE v5.0 and recorded on the eCRF with appropriate disease/condition terms.

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 (Appendix 6).

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

7.5.3 Eastern Cooperative Oncology Group Performance Status

ECOG PS (Appendix 2) will be assessed during the study.

7.5.4 Laboratory Safety Tests

Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, total creatinine kinase (CK) and creatine kinase cardiac muscle isoenzyme (CK-MB), and urinalysis will be conducted. The same laboratory should be used throughout the study for each patient, except in emergency situations. Certain elements will be collected as specified below:

If laboratory tests at screening are not performed within 7 days prior to randomization, these tests should be repeated and reviewed before randomization. Hematology and serum chemistry (including liver function tests) will be performed and reviewed prior to dosing of each treatment cycle, as clinically indicated, and upon discontinuation of chemotherapy. Total CK and CK-MB will be assessed for all patients (including the patients who will be receiving tislelizumab after crossover) at screening, at scheduled visits during treatment cycles and at the end of treatment and safety follow up visits (data collected as specified in Section 7.5.4). After Cycle 1, results are to be reviewed within 48 hours before study drug administration. Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study drug administration.

Local laboratory assessments will include the following:

- Hematology (complete blood count [CBC], including red blood cell [RBC] count, hemoglobin, hematocrit, WBC count with differential [neutrophils], 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, CK, and CK-MB)Note: Serum CK and CK-MB testing will be implemented for all patients at screening, at scheduled visits and at the end of treatment and safety follow up visits. The same schedule for serum CK and CK-MB testing will be applied for patients who receive tislelizumab after crossover upon confirmed disease progression on chemotherapy arm. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead.

- Coagulation test (international normalized ratio, prothrombin time, and activated partial thromboplastin time)
- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation) within 7 days prior to randomization. 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
- 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). Thyroid function tests will be performed at screening and every 3 cycles (ie, Cycles 4, 7, 10, etc), and at the Safety Follow-up visit.
- Total CK and CK-MB assessment (ECG, serum troponins, and other examinations as clinically indicated and as appropriate, if significant abnormalities are detected)

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision.

7.5.5 Electrocardiograms

The ECG recordings will be obtained during screening, the Safety Follow-up visit, and as clinically indicated.

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.

When coinciding with blood draws at the same timepoint, ECG assessment should be performed prior to blood draws. Patients should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

7.5.6 Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE, Version 5.0 (NCI-CTCAE 2017). Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.5.7 Hepatitis B and C Testing

Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). The HBV DNA test will be performed only for patients who have a positive antibody to

hepatitis B core antigen (anti-HBc antibody) test. The HCV RNA test will be performed only for patients who test positive for HCV antibody.

7.6 Tumor and Response Evaluations

Tumor imaging will be performed within 28 days before randomization. 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. During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remaining 6 months of Year 1, and after completion of the Week 52 tumor assessment, tumor assessment will continue every 12 weeks (± 7 days) based on RECIST v1.1.

Screening assessments and each subsequent assessment must include computed tomography (CT) scans (with oral/IV contrast, unless contraindicated) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

Tumor assessments must include CT scans (with oral/IV contrast, unless contraindicated) or 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. 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). All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

- Imaging of the brain (MRI or CT) at baseline (≤ 28 days of informed consent) is required for all screened patients.
- For patient with known and previously treated brain metastases, the scan should be within 14 days of randomization.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis 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 PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans afterwards, or if clinically indicated, Tc-99m or PET bone scans should be repeated when a complete response (CR) is suspected 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, if there is evidence of metastatic disease in these regions at

screening. At the investigator's discretion, other methods of assessment of target lesions and nontarget lesions per RECIST v1.1 may be used.

Response will be assessed by the IRC and the investigator using RECIST v1.1 (Appendix 3). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment timepoint.

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). The following criteria must be met to treat patients with suspected pseudoprogression:

- 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, death, or until the study terminates, whichever occurs first.

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

7.7 Pharmacokinetic and Antidrug 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 timepoints throughout the study (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.

The following assessments will be performed at a central laboratory:

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

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

7.8 Biomarkers

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

Archival tumor tissue (FFPE or approximately 15 [at least 6] unstained slides) must be sent to central laboratory for central immunohistochemistry assessment of PD-L1 status. If submitted tumor tissue is unevaluable for PD-L1 expression status, which might be due to an inadequate number of TCs, no TCs present, or tissue sections for central IHC assessment are not stainable, patients are still eligible to participate in the study and will be included in the < 1% TC group. In addition to PD-L1 expression, other exploratory predictive biomarkers, such as tumor mutation load and immune-related GEP that are related to response or clinical benefit of tislelizumab may also be evaluated. If no 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.

Optional biopsies will also be taken for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism. If feasible, any follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

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.

Optional blood samples will be taken at baseline (predose at Day 1 of Cycle 1), at the time of first tumor response (predose at Day 1 of the following Cycle), and at the Safety Follow-up visit after disease progression (10 mL each timepoint) for the Patients who have randomized in Arm A and Arm B to explore the association with response, resistance, and prognosis to tislelizumab in combination with chemotherapy. Written patient consent is required for blood sample collections.

7.9 Patient-Reported Outcomes

Patients will be asked to complete the EORTC QLQ-LC13, EORTC QLQ-C30 questionnaires before any clinical activities are performed during on-study clinic visits according to the schedule in Appendix 1. 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 (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 before study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date. The visit window is provided in Appendix 1.

7.11 Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the 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 the investigator's 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 monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1 Risks Associated With Study Drug

8.1.1 Risks Associated With Tislelizumab

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

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.3.

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

8.1.2 Risks Associated With Cisplatin/Carboplatin and Pemetrexed

For NSCLC patients who were treated with cisplatin/pemetrexed in a first-line setting, frequent (>5%) Grade 3 or 4 drug-related toxicities were neutropenia, anemia, nausea, vomiting, and fatigue (Scagliotti et al 2008). For NSCLC patients who were treated with carboplatin in a first-line setting, frequent (> 5%) Grade 3 or 4 toxicities were leukopenia, neutropenia, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, anorexia and constipation (Ohe et al 2007). Although not life-threatening, these AEs can severely impact the physical, psychological, and social wellbeing of patients receiving chemotherapy and can lead to dose reductions and discontinuations.

Please refer to Table 2 below for the reported toxicity of the respective chemotherapeutic agents. The investigator should refer to the respective prescribing information for additional details.

Table 2. The Summary of the Commonly and Specific Reported Toxicity of the Chemotherapeutic Agents

Agents	Common Toxicity	Specific Toxicity
Cisplatin	myelodepression with leukopenia, thrombocytopenia and anemia; infectious complications; nausea/vomiting and other GI toxicity; hepatic impairment; fatigue; anorexia; constipation	Nephrotoxicity; ototoxicity; peripheral neuropathies
Carboplatin		Ototoxicity and peripheral neuropathies
Pemetrexed		Nephrotoxicity; skin rash

8.2 General Plan to Manage Safety Concerns

8.2.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases, or with a history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation and patients who have received a live viral vaccine within 28 days before randomization are excluded from the study. Patients with contraindications for platinum doublet

chemotherapy treatment are also excluded from the study. Refer to Section 4.2 for the full list of exclusion criteria.

8.2.2 Safety Monitoring Plan

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

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

Serum samples will be drawn for determination of ADAs to tislelizumab in patients randomized to the tislelizumab arm. 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 (Section 5.2.1).

All AEs will be recorded during the study (AEs 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 study drug, including platinum doublet chemotherapy, 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 AE.

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

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

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

8.3 Adverse Events

8.3.1 Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2 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 v5.0.

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

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

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.3.

8.3.3 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of

the AE or SAE to the study drug should be considered and investigated. The investigator should consult the tislelizumab Investigator's Brochure in the determination of his/her assessment.

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

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

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as not related:
- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely

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

8.3.4 Following Adverse Events

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

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

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient

withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

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

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

8.3.5 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count [CBC], coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the 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.
- If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g, alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e, cholestasis) should be recorded on the Adverse Event eCRF.
- If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”
- Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4 Definition of a Serious Adverse Event

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

- Results in death
- Is life threatening

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

- Requires hospitalization or prolongation of existing hospitalization

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

- Results in disability/incapacity

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

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical 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

8.5 Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1 Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. An irAE (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.

8.6.2 Reporting Serious Adverse Events

8.6.2.1 Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 3.

Table 3. Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

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

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

8.6.2.2 Completion and Transmission of the Serious Adverse Event Report

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

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

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

The sponsor will provide contact information for SAE receipt.

8.6.2.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

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

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

8.6.3 Eliciting Adverse Events

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

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

8.6.4 Recording 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."

8.6.5 Deaths

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

8.6.6 Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 120 days after the last dose of tislelizumab or within 30 days after the last dose of chemotherapy agents a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

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

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

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

- Tislelizumab Investigator's Brochure
- Cisplatin/Carboplatin label
- Pemetrexed label

8.6.8 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 (Section 8.7.3) 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 CPIs, in Appendix 6.

An extensive list of potential irAEs appears in Section 8.7.3, Table 5. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 6.

8.7 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 criteria are outlined below.

8.7.1 Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 4.

Table 4. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

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

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

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

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

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

8.7.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen [which should be avoided in patients with CrCl between 45 and 79 mL/min for 2 days before, the day of, and 2 days following administration of pemetrexed], 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.

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

Recommendation for diagnostic evaluation and management of irAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen et al 2017, Brahmer et al 2018) and common immune-related toxicities are detailed in Appendix 6. For any AEs not included in Appendix 6, 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 5. Immune-Related Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

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

Recommendations for managing irAEs is detailed in Appendix 6.

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

8.7.4 Renal Function Abnormalities

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

- If the serum creatinine is normal at baseline, please see Section 8.7.3 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 8 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the eGFR falls below 20 mL/min/1.73 m^2.
- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with tislelizumab, refer to Appendix 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 SAMPLE SIZE DETERMINATION

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

9.1 Statistical Analysis

9.1.1 Randomization Methods

As discussed in Section 7.2.3, patients will be randomized using the IRT system for this study by permuted block stratified randomization with stratification factors of Stage (IIIB versus IV) and PD-L1 expression in TC (≥ 50% TC versus 1%-49% TC versus < 1% TC).

The stratified randomization will be produced, reviewed, and approved by an independent statistician.

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 Per-Protocol (PP) analysis set includes randomized patients who received at least 1 dose of the assigned study drug and had no major protocol deviations. Major protocol deviations will be determined and documented before the database lock for the primary analysis.

The Safety analysis set includes all randomized patients who received at least 1 dose of study drug; it will be the population for the safety analyses.

The PK analysis set includes all patients who receive at least 1 dose of tislelizumab per the protocol, for whom any post-dose PK data are available.

The immunogenicity (ADA) analysis set includes all patients who received at least 1 dose of tislelizumab for whom both baseline ADA and at least 1 post-baseline ADA results are available.

9.1.3 Patient Disposition

The number of patients randomized, treated, and 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 cut-off 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 will be summarized in the ITT analysis set 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 neoadjuvant or adjuvant therapy; stage of disease; PD-L1 expression in TC; gender; ECOG PS; race; smoking status; prior systemic therapies; and metastatic site.

9.1.5 Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the day of 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 the Safety Follow-up visit). In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an

irAE or is a new anticancer therapy) at 60 and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2 Efficacy Analyses

9.2.1 Primary Efficacy Analysis

PFS per the IRC in the ITT analysis set:

PFS per the IRC is defined as the time from randomization to the first documented disease progression as assessed by the IRC with the use of RECIST v1.1, or death from any cause, whichever occurs first. 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 without post-baseline tumor assessment will be censored at the time of randomization. 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 loss 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.

PFS per the IRC will be compared between tislelizumab with platinum-pemetrexed (Arm A) and platinum-pemetrexed alone (Arm B) in a stratified log-rank test at one-sided significance level α=0.025.

The null hypothesis to be tested is: H_0: PFS in Arm A ≤ PFS in Arm B

Against the alternative hypothesis: H_a: PFS in Arm A > PFS in Arm B

The p-value from a stratified log-rank test will be presented using stratification factors. The median PFS will be calculated for each treatment arm and presented with two-sided 95% confidence intervals (CIs). Kaplan-Meier survival probabilities for each arm will be plotted over time. The hazard ratio (HR) between Arm A and Arm 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 as recorded in the eCRF.

Subgroup analysis of primary endpoint of PFS per the IRC will be conducted to determine if the treatment effect is consistent across various subgroups, the HR estimates of PFS and its 95% CI will be estimated and plotted within each category of the following variables: PD-L1 expression in TC (≥ 50% TC versus 1%-49% TC versus < 1% TC), Stage (IIIB versus IV), age (≤ 65 versus > 65 years), gender (female versus male), ECOG PS (0 versus 1), and smoking status (Former versus Current versus Never).

The analysis of PFS per the IRC in the PP analysis set may be conducted as sensitivity analysis.

9.2.2 Secondary Efficacy Analysis

Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization.

Similar methodology used to evaluate PFS per the IRC will be applied to OS analysis.

Progression-free survival per the investigator

PFS per the investigator is defined as the time from randomization to the first objectively documented disease progression, or death from any cause, whichever occurs first, as determined per RECIST v1.1 in an ITT analysis set. Similar methodology used to evaluate PFS per the IRC will be applied to analysis of PFS per the investigator.

Overall response rate per the IRC

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had a CR or PR as assessed by the IRC per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment will be considered non-responders. The difference in ORR between arms in the ITT analysis set will be evaluated using the Cochran-Mantel-Haenszel (CMH) 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.

Overall response rate per the investigator

ORR (confirmation not required according to RECIST v1.1) is the proportion of patients who had a CR or PR as determined by the investigator per RECIST v1.1 in ITT analysis set. Patients without any post-baseline assessment will be considered non-responders. Similar methodology used to evaluate ORR per the IRC will be applied to analysis of ORR per the investigator.

Duration of response per the IRC

DOR per the IRC is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as assessed by the IRC using the RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. DOR will be estimated using Kaplan-Meier methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

Duration of response per the investigator

DOR per the investigator is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator using the RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. Similar methodology used to evaluate DOR per the IRC will be applied to analysis of DOR per the investigator.

Health-Related Quality of Life

Summary statistics (mean, SD, median, and range) of the post-baseline scores will be reported for the EORTC Quality of Life Cancer Questionnaire (EORTC QLQ-LC13 and EORTC QLQ-C30). The mean change of the scores from baseline (and 95% CI with use of the normal approximation) will also be assessed. Line charts depicting the mean changes (and standard errors) over time from the baseline assessment will be provided for each treatment arm. The proportion of patients showing clinically meaningful change in selected items and subscales at each assessment timepoint will be calculated. Completion and compliance rates will be summarized at each timepoint by treatment arm. Only patients with a non-missing baseline assessment and at least one in-study non-missing post-baseline assessment will be included in the analyses. Summaries will be performed for the ITT analysis set only.

PD-L1 expression as a predictive biomarker for response

Distribution of PD-L1 expression in TC will be examined in the ITT analysis set. Association between PD-L1 expression and tislelizumab treatment effect over control (PFS, OS, ORR, DOR, DCR) will be explored.

9.2.3 Exploratory Efficacy Analysis

Disease control rate per the investigator

DCR is defined as the proportion of patients with objective response (CR or PR) or stable disease (SD) maintained for ≥ 6 weeks as determined by the investigator using the RECIST v1.1. The analysis methods for DCR will be the same as those for ORR per the investigator.

Time to response per the investigator

TTR per the investigator is defined for patients with an objective response as determined by the investigator as the time from randomization to the first occurrence of a CR or PR as determined by the investigator using the RECIST v1.1. TTR will be summarized for descriptive purposes. The mean, standard error, median, and range of TTR will be provided.

9.3 Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. 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), and relative dose intensity.

The number (percentage) of patients requiring dose reduction, 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 (the investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 20.0 or higher) by lower-level term, preferred term, and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug and up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. For the tislelizumab arm, the TEAE classification also applies to irAEs that are recorded up to 90 days from the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v5.0 within an SOC and preferred term, even if the patient experienced > 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose interruption, dose reduction, or dose delay will be summarized.

9.3.3 Laboratory Analyses

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

Laboratory parameters that are graded in NCI-CTCAE v5.0 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, glucose, potassium, sodium) will be summarized separately.

9.3.4 Vital Signs

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

9.4 Pharmacokinetic Analysis

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

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

Additional PK analyses, including population PK analyses and exposure-response (efficacy, safety endpoints) analyses may be conducted as appropriate and the results from these analyses will be reported separately from the CSR.

9.5 Sample Size Consideration

The sample size calculation is based on the number of events required to demonstrate the PFS superiority of Arm A to Arm B in the ITT analysis set.

The estimates of the number of events required to demonstrate efficacy about PFS in the primary comparisons are based on the following assumptions:

1. Median PFS of 7 months in Arm B with exponential distribution assumption.
2. At a one-sided α of 0.025, 85% power to detect an HR of 0.65, corresponding to an improvement in median PFS from 7 months to 10.8 months, in the ITT analysis set.
3. Randomization ratio of 2:1.
4. One interim analysis of PFS planned in the ITT analysis set when approximately 71% of total PFS events occurred, with Lan-DeMets' approximation to O'Brien-Fleming boundary (O'Brien et al, 1979).

With these assumptions, a total of 215 PFS events is required for the ITT analysis set for the PFS final analysis. Assuming 320 patients are to be enrolled over an 8-month period at a constant enrollment rate, the PFS final analysis will occur approximately 19.2 months after the first patient is randomized.

9.6 Interim Analyses

There will be 1 interim efficacy analysis of PFS performed in the ITT analysis set. The interim efficacy analysis of PFS will be performed when approximately 153 PFS events (71% of the targeted number of 215 PFS events) are observed in the ITT analysis set. It is estimated that it will take approximately 12.8 months to observe 153 PFS events.

The interim boundary for PFS is based on the Lan-DeMets approximation to O'Brien-Fleming boundary. The interim and final analysis timing and stopping boundaries are summarized in Table 6, and the exact time of each analysis will depend on actual number of events occurred.

Table 6. Analysis Timing and Stopping Boundary for PFS in the ITT Analysis Set (overall one-sided hypothesis testing at α = 0.025)

Type of Analysis	Time (Months)	Number of Events	Testing Boundary	
			P-value Boundary	Approx. HR Threshold
Interim analysis	12.8	153	0.0078	0.660
Final analysis	19.2	215	0.0226	0.748

9.7 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 ADA in the ADA analysis set. 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.

10 STUDY COMMITTEES AND COMMUNICATION

10.1 Blinded Independent Central Review

A Blinded Independent Review Committee (BIRC) will be established to perform an independent review of all radiological images for the efficacy analysis and to determine all instances of response and disease progression based on the RECIST v1.1 criteria, in addition to the local investigator review of radiographs. The results from the investigator's review of radiographic images will be used to determine whether patients should be enrolled or should

continue study treatment. The tumor assessment by the BIRC will be used for the reporting of the study results.

All decisions made during the performance of the study will be based on the local investigator's assessment of radiographic images, clinical status, and relevant examination of the patients. Sites will submit specific radiographic image files to the centralized data review facility during the study at an ongoing basis or at the sponsor's request. Detailed rules and guidelines for radiographic imaging and tumor assessments by the BIRC are outlined separately in the Imaging Manual and the BIRC Charter.

10.2 Independent Data Monitoring Committee

Regular safety monitoring (approximately every 6 months) and efficacy monitoring will be performed by an Independent Data Monitoring Committee (IDMC). The first IDMC safety review will occur after ≥ 30 patients have been randomized to study treatment and have been on treatment for ≥ 1 month or have completed at least 1 cycle of study treatment to determine whether the proposed dosing schedule of tislelizumab is safe and tolerable. The IDMC may recommend study modification including termination of the study due to safety and/or efficacy concerns. 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 Council for Harmonisation (ICH) GCP guidelines, the study monitor must have direct access to the investigator's source documentation 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 while 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 study with the investigational drug from the China regulatory agency in accordance with applicable regulatory requirements in China before the study is initiated at a study center.

12.2 Quality Assurance

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

12.3 Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, 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 to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4 Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient 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 batch/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 requirements specified in the Pharmacy Manual. At appropriate time during the conduct of the study or at the end of the study, the study site will dispose of and/or destroy all unused study drug supplies following drug inventory reconciliation by the monitor. These include 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 ETHICS/PROTECTION OF HUMAN PATIENTS

13.1 Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice (ICH E6 [R2] 2016) and the principles of the Declaration of Helsinki (Declaration of Helsinki 2013) 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) (ICH E2A 1994).

13.2 Institutional Review Board/Independent Ethics Committee

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

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

13.2.1 Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/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/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 ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

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

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

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

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

13.4 Patient and Data Confidentiality

The sponsor will maintain confidentiality and privacy standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

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

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

Data generated by this study must be available for inspection upon request by representatives of the US Food and Drug Administration (FDA), the China FDA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs 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 the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the IND, and any other study information, remains 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 the 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 about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection and Management Responsibilities

14.1.1 Data Collection

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

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all

clinical data entered in the eCRF. The investigator 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.

AEs will be coded using the MedDRA Version 20.0 or higher. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.0 or higher.

14.2 Data Integrity and In-house Blinding

Due to the open-label design of the study, access to the patient level clinical data in the 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 from the EDC system with other functions/persons who do not have access to the EDC. In addition, the central imaging vendor will perform the central imaging review without knowledge of treatment arm assignment. Although the study is open label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented.

14.3 Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should

be classified into at least 1 of the following categories: 1) the investigator's study file and/or 2) the patient clinical source documents.

The investigator's study file will contain the protocol/amendments, 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 documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

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

The sponsor will inform the investigator of the 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 5 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to archival at an off-site facility or 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 is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

14.5 Publication and Data-Sharing Policy

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

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (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 Uniform Requirements for Manuscripts or stricter local criteria (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 study 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 or suspend enrollment either at a single study center or at all study centers at any time for reasons including but not limited to safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

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

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for 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 while or because 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 confidential by the investigator and other study center personnel.

This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information 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 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.

15 REFERENCES

ALECENSA® (alectinib) [prescribing information] South San Francisco, CA; Genentech, Inc.

ALIMTA® (pemetrexed) [prescribing information] Indianapolis, IN; Eli Lilly and Company

American Cancer Society. Non-Small Cell Lung Cancer. https://www.cancer.org/cancer/non-small-cell-lung-cancer.html. Accessed 07 February 2017.

Antonia S, Ou S, Khleif S, et al. Clinical activity and safety of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer. Ann Oncol. 2014;25(suppl 4):426–70.

Antonia SJ, López-Martin J, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet. 2016;17:883-95.

Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. N Engl J Med. 2017; Sep 8. Epub ahead of print.

Apolo AB, Infante JR, Balamanukian A, et al. Avelumab, an anti–programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol. 2017;35(19):2117-24.

Ardizzoni A, Boni L, Tiseo M, et al. Cisplatin versus carboplatin-based chemotherapy in first-lin treatment of advanced non-small cell lung cancer: an individual patient data meta-analysis. J Nat Cancer Inst. 2007;99:847-57.

Azzoli CG, Baker Jr S, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for Stage IV non-small cell lung cancer. J Clin Oncol. 2009;27:6251-66.

Basch E, Wood WA, Schrag D, et al. "Feasibility and clinical impact of sharing patient-reported symptom toxicities and performance status with clinical investigators during a phase 2 cancer treatment trial." Clin Trials. 13.3 (2016): 331-7.

BeiGene (2017). [BGB-A317_Study_001]. Data on file.

BeiGene Investigator's Brochure, tislelizumab. Edition 5.0, February 2018.

Bersanelli M, Buti S. From targeting the tumor to targeting the immune system: transversal challenges in oncology with the inhibition of the PD-1/PD-L1 axis. World J Clin Oncol. 2017;8(1):37-53.

Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non- small-cell lung cancer. N Engl J Med. 2015; 373:1627–39.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373(2):123-35.

Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018. [E-pub ahead of print]

Chen W, Zheng R, Baade P, et al. Cancer statitistics in China, 2015. CA Cancer J Clin 2016;66(2):115-32.

Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small cell lung cancer: a randomised, double-blind, phase 3 study. Lancet. 2009;374:1432-40.

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

Cohen MH, Gootenberg L, Keegan P, et al. FDA Drug Approval Summary: Bevacizumab (Avastin) Plus Carboplatin and Paclitaxel as First-Line Treatment of Advanced/Metastatic Recurrent Nonsquamous Non-Small Cell Lung Cancer. Oncologist. 2007;12:713–8.

Dajczman E, Kasymjanova G, Kreisman H, et al. "Should patient-rated performance status affect treatment decisions in advanced lung cancer?" J Thorac Oncol. 3.10 (2008): 1133-6.

de Castria TB, da Silva EM, Gois AF, et al. Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer. Cochrane Database Syst Rev 2013(8):CD009256.

Dolgin M, Association NYH, Fox AC, Gorlin R, et al. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994

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):228-47.

Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32:1277-80.

European Medicines Agency Guideline on the evaluation of anticancer medicinal products in man. EMA/CHPM/205/95/Rev.4 (December 2012).

Fennell DA, Summers Y, Cadranel J, et al. Cisplatin in the modern era: the backbone of first-line chemotherapy for non-small cell lung cancer. Cancer Treat Rev. 2016;44:42-50.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015 Mar 1;136(5).

Food and Drug Administration. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. May 2007. Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071590.pdf

Food and Drug Administration. Product labels for FDA approved drug products are available online: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed 01 February 2017a.

Food and Drug Administration. Approved Drugs. Avelumab (BAVENCIO). https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm547965.htm. Accessed 25 December 2017b.

Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase 3 study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003;21:3016-24.

Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a Phase 3, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011;29:2866-74.

Gandhi L, Rodriguez-Abreu, D, Gadgeel, S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. 2018; published on April 16, 2018.

Garon EB, Gandhi L, Rizvi N, et al. Antitumor activity of pembrolizumab (PEMBRO; MK-3475) and correlation with programmed death ligand 1 (PD-L1) expression in a pooled analysis of patients (pts) with advanced non-small cell lung carcinoma (NSCLC). Ann Oncol. 2014;25(suppl 4, 1 September):1–41.

Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372:2018-28.

Gaschler-Markefski B, Sikken P, Heymach JV, et al. "Time since start of first-line therapy as a predictive clinical marker for nintedanib in patients with previously treated non-small cell lung cancer." ESMO Open 2.1 (2017): e000102.

Gettinger SN, Horn L, Gandhi L, et al. "Overall survival and long-term safety of nivolumab (anti–programmed death 1 antibody, BMS-936558, ONO-4538) in patients with previously treated advanced non–small-cell lung cancer." J Clin Oncol. 2015;33(18):2004-12.

Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2(8):706-14.

Gong W, Song Q, Lu X, et al. Paclitaxel induced B7-H1 expression in cancer cells via the MAPK pathway. J Chemother. 2011;23(5):295–9.

Gou LY, Wu YL. Prevalence of driver mutations in non-small-cell lung cancers in the People's Republic of China. Lung Cancer: Targets and Therapy. 2014;5:1-9.

Haanen JBAG, Carbonnel F, Robert C, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol. 2017:28 (suppl 4):iv119-iv142.

Hellmann MD, Gettinger SN, Goldman JW, et al. "CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC." 2016; 34 (suppl 15):3001.

Hellmann M, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18:31-41.

Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014;515:563–7.

Herbst RS, Baas P, Perez-Gracia JL, et al. PD1. 06 (also presented as P2. 41): pembrolizumab vs docetaxel for previously treated NSCLC (KEYNOTE-010): archival vs new tumor samples for PD-L1 assessment. Journal of Thoracic Oncology. 2016 Oct 1;11(10):S174-5.

Hodi FS, Chesney J, Pavlick AC, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;17(11):1558-68.

Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small cell lung cancer. J Clin Oncol. 2004;22:3852-9.

ICH harmonised guideline - Clinical safety data management: definitions and standards for expedited reporting E2A: current step 4 version, 27 October 1994: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf

ICH harmonised guideline - Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2): current step 4 version, 9 November 2016: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf

International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2016. Available online: http://www.icmje.org. Accessed 08 August 2017.

Jiang L, Yang K, Mi D, et al. Safety of irinotecan/cisplatin versus etoposide/cisplatin for patients with extensive-stage small-cell lung cancer: a metaanalysis. Clin Lung Cancer. 2007;8:497-501.

Jin Z, Yoon HH. The promise of PD-1 inhibitors in gastro-esophageal cancers: microsatellite instability vs. PD-L1. J Gastrointest Oncol. 2016;7(5):771-88.

Kelly K, Crowley J, Bunn PA Jr, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol. 2001:19(13):3210-18.

Kerr K, Tsao M, Nicholson A et al. Programmed death-ligand 1 immunohistochemistry in lung cancer: In what state is this art? J Thorac Oncol. 2015;10:985–89.

Keytruda [prescribing information]. Foster City, CA: Gilead Sciences, Inc; 2014.

Koren E, Smith HW, Shores E, et al. Recommendations on risk-based strategies for detection and characterization of antibodies against biotechnology products. J Immuno Methods. 2008;333:1-9.

Labrijn AF, Buijsse AO, van den Bremer ET, et al. Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo. Nat Biotechnol. 2009;27(8):767-71.

Langer C, Gaddgeel SM, Borghaei H, et al. "Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021 cohort G." 2016;27(6)(suppl):LBA46_PR.

Laporte S, Squifflet P, Baroux N, et al. Prediction of survival benefits from progression free survival benefits in advanced non-small cell lung cancer: evidence from a meta-analysis of 2334 patients from 5 randomized trials. BMJ Open. 2013;3:1-6.

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

McDaniel AS, Alva A, Zhan T, et al. Expression of PD-L1 (B7-H1) before and after neoadjuvant chemotherapy in urothelial carcinoma. Euro Urol Focus. 2016;1(3):265–8.

Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803-3.

National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Published: May 28, 2009 (v5.0: November 27, 2017). U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES. National Institutes of Health. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed 25 December 2017.

National Comprehensive Cancer Network: NSCLC Guidelines v7: 2017. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#nscl

O'Brien, P.C.; Fleming, T.R.. A Multiple Testing Procedure for Clinical Trials. Biometrics. 1979: 549–56

Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol. 2007; Feb;18(2):317-23.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

Ono Pharmaceutical Co, Ltd. Available online: https://www.ono.co.jp/eng/news/pdf/sm_cn161227.pdf. Accessed 01 February 2017.

Patel JD, Socinski MA, Garon EB, et al. PointBreak: A randomized phase 3 study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small-cell lung cancer. J Clin Oncol. 2013;31:4349-57.

Patel SP, Kurzrock R. PD-L1 Expression as a predictive biomarker in cancer immunotherapy. Mol Cancer Ther. 2015;14(4):847–56.

PDQ Adult Treatment Editorial Board. Small Cell Lung Cancer Treatment (PDQ®): Health Professional Version. 2018 Apr 20. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002. https://www.ncbi.nlm.nih.gov/books/NBK65909/. Accessed 21 December 2017.

Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol. 2012 Mar 31;13(3):247-55.

Paz-Ares L, de Marinis F, Dediu M, et al. PARAMOUNT: final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non–small-cell lung cancer. J Clin Oncol. 2013 Aug 10;31(23):2895-902.

Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005; 26: 948–968.

Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised Phase 3 trial (AVAiL). Ann Oncol. 2010;21:1804-9.

Reck M, Rodriguez-AbreuD, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1 positive non-small cell lung cancer. N Eng J Med. 2016;375:1823-33.

Reck M, Socinski MA, Cappuzzo F, et al. LBA1_PR Primary PFS and safety analyses of a randomized phase III study of carboplatin+ paclitaxel+/− bevacizumab, with or without atezolizumab in 1L non-squamous metastatic nsclc (IMPOWER150). Annals of Oncology. 2017 Dec 1;28(suppl_11):mdx760-002.

Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.

Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015;1693):257-65.

Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non–small-cell lung cancer. Journal of Clinical Oncology. 2016 Jun 27;34(25):2969-79.

Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first line treatment for European patients with advanced EGFR mutation-positive non small cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012;13:239-46.

Roviello G, Bachelot T, Hudis CA, et al. The role of bevacizumab in solid tumours: A literature based meta-analysis of randomised trials. Eur J Cancer. 2017;75:245-58.

Sandler S, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542-50.

Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum- based doublets in advanced non-small-cell lung cancer. J Clin Oncol. 2002;20:4285-91.

Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:3543–51.

Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med. 2002;346:92–8.

Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. Journal of clinical oncology. 2013 Jul 1;31(27):3327-34.

Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non–small-cell lung cancer. New England Journal of Medicine. 2014 Nov 20;371(21):1963-71.

Shih C, Chen VJ, Gossett LS, et al. LY231514, a pyrrolo[2,3-d]pyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res. 1997;57:1116-23.

Soar J, Pumphrey R, Cant A, et al. Emergency treatment of anaphylactic reactions--guidelines for healthcare providers. Resuscitation. 2008;77(2):157-69.

Socinski M, Creelan B, Horn L, et al. "NSCLC, metastatic CheckMate 026: A phase 3 trial of nivolumab vs investigator's choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)−positive NSCLC." Annals Oncol. 2016;27(suppl 6).

Stinchcombe TE, Socinski MA. "Considerations for second-line therapy of non-small cell lung cancer." Oncologist. 2008;13(suppl 1):28-36.

Tecentriq [prescribing information]. San Francisco, CA: Genentech, Inc; 2017.

Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan;63(1):261-83.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443-54.

Van Der Kraak L, Goel G, Ramanan K, et al. 5-Fluorouracil upregulates cell surface B7-H1 (PD-L1) expression in gastrointestinal cancers. J Immunother Cancer. 2016; 4(1):65.

Wang C, Thudium KB, Han M, et al. In vitro characterization of the anti-PD-1 antibody nivolumab, BMS-936558, and in vivo toxicology in non-human primates. Cancer Immunol Res. 2014;2(9):846-56.

Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16:375-84.

WMA Declaration of Helsinki – ethical principles for medical research involving human subjects, 19 Oct 2013: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Worobec AS and Rosenberg AS. A risk-based approach to immunogenicity concerns of therapeutic protein products, Part 1: Considering consequences of the immune response to a protein. BioPharm Int. 2004a;(17).

Worobec A, Rosenberg AS. A risk-based approach to immunogenicity concerns of therapeutic protein products, Part 2: Considering host-specific and product-specific factors impacting immunogenicity. BioPharm Int. 2004b;(17). http://www.biopharminternational.com/risk-based-approach-immunogenicity-concerns-therapeutic-protein-products-part-2-considering-host-spe. Accessed 01 August 2017.

XALKORI® (crizotinib) [prescribing information]. New York, NY; US: Pfizer, Inc.

Zhou F and Zhou C-C. Targeted therapies for patients with advanced NSCLC harboring wild-type EGFR: what's new and what's enough. Chin J Cancer. 2015. DOI: 10.1186/s40880-015-0036-4.

Zinner RG, Obasaju CK, Spigel DR, et al. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed+ carboplatin followed by maintenance pemetrexed versus paclitaxel+ carboplatin+ bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non–small-cell lung cancer. Journal of Thoracic Oncology. 2015 Jan 31;10(1):134-42.

ZYKADIA® (ceritinib) [prescribing information]. East Hanover, New Jersey; Novartis Pharmaceuticals Corporation.

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 6 (Every 21 days)			Cycle 7 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 (± 14 Days)**
Informed consent	x							
Inclusion/exclusion criteria	x							
Randomization		x[5]						
Demographics/medical history/prior medications[6]	x							
Vital signs/ height and weight[7]	x	x			x	x	x	
Physical examination[8]	x	x			x	x	x	
ECOG Performance Status	x	x			x	x	x	
12-lead ECG[9]	x						x	
Adverse events[10]	x	x	x[24]	x[24]	x	x	x	x
Concomitant medications	x	x	x[24]	x[24]	x	x	x	
Hematology[11]	x[1]	x			x	x[2]	x	
Serum chemistry[11]	x[1]	x			x	x[2]	x	
Coagulation parameters[11,12]	x	x			x	x[2]	x	
Total CK and CK-MB[11a]	x[1]	x			x	x[2]	x	
Urinalysis[11]	x	As clinically indicated						
Pregnancy test[13]	x				x			

Assessment	Screening[1]	Treatment Cycles					Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 6 (Every 21 days)			Cycle 7 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 (± 14 Days)**
Thyroid function (every 3 cycles)[14]	x[1]	x[14]			x[14]		x	
HBV/HCV tests[15]	x	As clinically indicated						
Pulmonary function tests[16]	x							
Pharmacokinetics[17]		x			x		x	
Anti-tislelizumab antibodies[18]		x			x		x	
Tumor assessment[19]	x				x	x[2]		x
Archival tumor tissue[20]	x							
Fresh tumor tissue [20]	x					x *(Optional tumor biopsy collection for patients with progressive disease)*		
Blood collection (for TMB)[21]		x			x		x	
Study drug administration [22]		x			x			
EORTC QLQ-C30[23]	x	x			x	x		
EORTC QLQ-LC13[23]	x	x			x	x		
Survival status								x

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK, creatine kinase; CK-MB, creatine kinase – cardiac muscle isoenzyme; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC QLQ-LC13, 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; EOT, End-of-Treatment (visit); FFPE, formalin-fixed paraffin-embedded; FSH, follicule-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; irAE, immune-related adverse event; IRB, Institutional Review Board; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; NCI-CTCAE, National Cancer Institute Common Terminology Criteria

for Adverse Events; PET, positron emission tomography; PK, pharmacokinetic; PO, orally; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TMB, tumor mutation burden; TSH, thyroid stimulating hormone; v, version.

1. Written informed consent is required prior to 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.
2. The End-of-Treatment (EOT) visit is conducted when the investigator determines that tislelizumab and/or chemotherapy will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT visit, tests need not be repeated. 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 is required to be conducted 30 days (± 7 days) after the last dose of tislelizumab or chemotherapy, or before the initiation of a new anticancer treatment, whichever occurs first. The End of Treatment (EOT) 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.
4. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the Safety Follow-up visit until death, loss to follow-up, withdrawal of consent, or study completion by sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
5. Patients will be randomized into either Arm A or Arm B via IRT. All patients are required to receive study treatment within 2 business days of randomization.
6. Includes age or date of birth, gender, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the investigator.
7. Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. The patient's vital signs are required to be recorded within 60 minutes before; during; and 30 minutes after the first two infusions of tislelizumab. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and, if clinically indicated, during and 30 minutes after the infusion. Height should be measured and recorded only during screening.
8. During the screening visit, a complete physical examination will be conducted. At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed.
9. The ECG recordings will be obtained during screening, the Safety Follow-up visit, and as clinically indicated at other timepoints. When coinciding with blood draws at the same timepoint, ECG assessment should be performed prior to blood draws. Patients should be resting in semi-recumbent supine position for ≥ 10 minutes prior to each ECG measurement.
10. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of 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 study drug(s) (including chemotherapy) or the initiation of new anticancer therapy, 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 or is a new anticancer therapy) at 60 days, and 90 days (± 14 days) after the last dose of study treatment, regardless of whether the patient starts a new anticancer therapy. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.
11. Local and/or central laboratory assessments of serum chemistry, hematology, coagulation, total CK and CK-MB and urinalysis will be conducted, of which certain elements will be collected as specified in Section 7.5.4. If laboratory tests at screening are not performed within 7 days prior to randomization, these tests should be repeated and reviewed before randomization. Hematology and serum chemistry (including liver function tests) will be performed and reviewed prior to dosing of each treatment cycle, as clinically indicated, and upon discontinuation of chemotherapy.(data collected as specified in Section 7.5.4). After Cycle 1, these laboratory tests are to be performed and reviewed within 48 hours before study drug administration.

Urinalysis is to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities. The safety assessments for patients who cross over to tislelizumab monotherapy should follow the schedule of Arm A Tislelizumab safety assessment procedure in Appendix 1.

a. Serum CK and CK-MB testing is included in total CK and CK-MB assessment, which will be implemented for all patients at screening, at scheduled visits, and at the end of treatment and safety follow up visits. The same schedule for serum CK and CK-MB testing will be applied for patients who receive tislelizumab after crossover upon confirmed disease progression on chemotherapy arm. In the event that CK-MB fractionation is not available, serum troponins (troponin I and/or T) measurements will be performed instead.

12. Includes international normalized ratio, prothrombin time, and activated partial thromboplastin time.
13. Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to randomization. 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.
14. Analysis of FT3, FT4, and TSH will be performed by a central laboratory or the local study site laboratory. 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.
15. Testing will be performed by a central laboratory and/or the local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). The HBV DNA test will be performed only for patients who have a positive antibody to hepatitis B core antigen (anti-HBc antibody) test. The HCV RNA test will be performed only for patients who test positive for HCV antibody.
16. 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.
17. PK samples will be collected only in patients randomized to receive tislelizumab and in sites that are able to adequately perform PK sampling, handling, and processing. For tislelizumab, predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9, and 17; a postdose (within 30 minutes after completing tislelizumab infusion) sample is required to be collected at Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the mandatory Safety Follow-up. Should a patient present with any ≥ Grade 3 irAE, an additional blood PK sample may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/ECs.
18. ADA samples will be collected only in patients randomized to receive tislelizumab combined chemotherapy patients and in sites that are able to adequately perform ADA sampling and handling. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17, and at the mandatory Safety Follow-up visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/ECs.
19. Radiological images captured as standard of care prior to obtaining written informed consent and within 28 days of randomization may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the screening visit. An MRI (or CT scan if MRI is contraindicated or not readily available) of the head is required at screening based on clinical judgment; bone scan or PET is required if clinically indicated. The same radiographic procedure must be used throughout the study for each patient.

    The investigator must review radiograph results before dosing at the next cycle. Patients will undergo tumor assessments approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for the remaining 6 months of Year 1, and every 12 weeks (± 7 days) after completion of the Week 52 tumor assessment onwards (based on RECIST v1.1 assessment). The investigator may perform additional scans or more frequent assessments if clinically indicated. See Section 7.6 for more information. 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 experiences disease progression, withdraws consent, dies, starts a new anticancer therapy, or until the study terminates, whichever occurs first.

20. Patients are required to provide archival tumor tissues (FFPE blocks or approximately 15 [at least 6] unstained slides) for biomarker analysis. Fresh biopsy: In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline is mandatory (written informed consent is required prior to fresh tumor biopsies). See Section 7.8 for more information. Patients who have progressive disease will be asked to provide optional biopsy for the assessment of mechanism of resistance (written informed consent is required prior to fresh tumor biopsy).
21. Optional blood samples will be taken at baseline (predose at Day 1 of Cycle 1), at the time of first tumor response (predose at Day 1 of the following Cycle) and at the Safety Follow-up visit after disease progression (10 mL each timepoint) for the patients who have been randomized into Arm A and Arm B to explore the association with response, resistance and prognosis to tislelizumab in combination with chemotherapy or chemotherapy alone. Written patient consent is required for blood sample collection.
22. Tislelizumab will be given by IV Q3W in Arm A. The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes and then can be administered over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for 1 hour after infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2. From Cycle 3 onward, at least a 30-minute monitoring period is required. Treatment could continue beyond progression if clinical benefit is seen and treatment is tolerated per the investigator's discretion. Patients should sign an informed consent form for continued treatment beyond RECIST v1.1 disease progression. Patients in Arm B who will be receiving tislelizumab following crossover after the IRC confirmed radiographic disease progression on chemotherapy should not initiate treatment with tislelizumab prior to resolution of treatment-related toxicities to ≤ Grade 1 or baseline, with the exception of select chemotherapy-related toxicities such as hair loss, but should be initiated within 42 days (if applicable), and upon consultation with the medical monitor. Refer to Section 7.4 for further specifications regarding crossover. Chemotherapy will be given by IV Q3W for patients in Arm A and Arm B until disease progression or unacceptable toxicity. In the maintenance phase, tislelizumab with pemetrexed will be given Q3W for patients in Arm A and pemetrexed alone will be given Q3W for patients in Arm B.
23. To be completed prior to any clinical activities during on-study site visits. EORTC QLQ-C30, and EORTC QLQ-LC13 will be completed at screening and/or baseline, at every other cycle through Cycle 13, then every 4 cycles thereafter, and at EOT.
24. a. Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15. The patient should be asked if any new symptoms have been observed or existing symptoms may have worsened, and if there has been any change to medications.

    b. All relevant information regarding an AE or SAE needs to be recorded in eCRF AE page. The corresponding medical test records (or appropriate copies) need to be sent and filed at the study site. The study site investigators need to remind patients to return to the clinical study site for further assessment if new AEs arise or worsen.

APPENDIX 2. ECOG PERFORMANCE STATUS

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

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

APPENDIX 3. 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):228-47.

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 nonmeasurable 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 examination (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 a 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 pertaining 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 based on their size (lesions with the longest diameter) and be representative of all involved organs, 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 during 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 (CR) 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 CR. 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 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: 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 progressive disease, 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 CR 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, to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and progressive disease, 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 can 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 be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints 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).
- progressive disease: 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- progressive disease: 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" based on 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 based on 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 applies 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 progressive disease 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 progressive disease 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 CR. 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 evidence of progressive disease 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 a new lesion, then progression should be declared using the date of the initial scan.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions based on 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 progressive disease 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 progressive disease. 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 progressive disease 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 based on the anatomic images, this is not progressive disease.

Evaluation of Best Overall Response

The BOR is the best response recorded from the start of the study drug treatment until the end of treatment considering 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR 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 nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The BOR 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 timepoints (for example, a patient who has SD at first assessment, PR at second assessment, and progressive disease on last assessment has a BOR 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 timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, progressive disease at second and does not meet minimum duration for SD, will have a best response of progressive disease. The same

patient lost to follow-up after the first SD assessment would be considered inevaluable.

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

Abbreviations: CR, complete response; NE, not evaluable; 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 timepoint 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 CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. 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 that 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 CR 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 progressive disease).

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 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 consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

APPENDIX 4. 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 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. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-related AE (irAE) are intended as 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 *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If patients experience acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan, for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal Toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, CK/CK-MB, echocardiogram, 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 work-up and treatment intervention, as appropriate, with patients is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms		Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline Grade.
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium	Hold study treatment; retreatment may be considered when resolved/improved to baseline Grade and after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	4 Life-threatening symptoms	supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin Reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical 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.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	or > 3-6X ULN	every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	
Ocular Toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/ panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4	Initiate IV (methyl)prednisolone	Discontinue study

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgment)	Study Drug Management
	Life-threatening complications or dehydration	not contraindicated by infection.	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 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to Grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	**< 2** Asymptomatic but significantly increased CK-MB, troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	**Hold study treatment** If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl) prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl) prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

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

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

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

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

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

where:

Scr is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

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

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

max indicates the maximum of Scr /κ or 1.

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

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/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 8. COCKCROFT-GAULT FORMULA AND CALVERT FORMULA

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

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

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

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

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

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

a Age in years and weight in kilograms.

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

CALVERT FORMULA:
(GFR*+25) × AUC= dose in mg
*GFR calculation formula is same as Cl_{Cr} formula as shown above.

NOTE: For patients with abnormally low serum creatinine level, estimate GFR using a minimum creatinine level of 0.8 mg/dL or cap the estimated GFR at 125 mL/min.

The FDA recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity due to overdosing. Based on the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

Maximum carboplatin dose (mg) = target AUC (mg/min/mL)*(GFR+25 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC=5, the maximum dose is 5*150=750 mg.

For a target AUC=4, the maximum dose is 4*150=600 mg.

Source: Follow-up for Information Letter Regarding AUC-based Dosing of Carboplatin (dated 22 October 2010).

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

Contraception Guidelines

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

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

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

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

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

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

- < 55 years of age with no spontaneous menses for ≥ 12 months AND with postmenopausal follicle-stimulating hormone concentration > 30 IU/mL 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 an FSH 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 10. DOSE MODIFICATION OF CHEMOTHERAPY

Recommended Dose Modifications for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration. Recommended dose modifications for hematologic toxicity are provided in Table 7.

Table 7. Chemotherapy Dose Modification[1] for Hematological Toxicity

Adverse Event		Treatment
Febrile neutropenia; documented infection		1) The first episode of febrile neutropenia or documented infection will result in antibiotic treatment and reduction by 25% of both drugs doses. 2) If there is a second episode despite dose reduction, the patient must receive prophylactic antibiotics during the subsequent cycles. 3) If there is a third episode, the chemotherapy will be discontinued.
Neutropenia	Grade 3 (0.5-0.99 x 10^9/L)	Chemotherapy delay until ≤Grade 1 (≥ 1.5 x 10^9/L); restart with the full dose
	Grade 4 (< 0.5 x 10^9/L)	Chemotherapy delay until recovered to ≤Grade 1; dose reduction of all further doses by 25%
Thrombocytonia	Grade 1	Chemotherapy delay until recovered to normal; restart with the full dose
	≥ Grade 2	Chemotherapy delay until recovered to normal; dose reduction of all further doses by 25%

1. If considered in the best interest of the patient and consistent with local practice, the investigators may decide to use supportive measures / treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only. Carboplatin is only permitted to reduce to -20% doses once (from AUC 5 to AUC 4).

Recommended Dose Modifications for Non-Hematologic Toxicities

The dose adjustments of chemotherapy for non-hematologic toxicity are described in Table 8. All dose modifications should be made based on the worst grade toxicity.

Table 8. Chemotherapy Dose Modifications for Non-Hematological Toxicity

Toxicity	Grade	Treatment
Renal toxicity	≥ Grade 1	Delay chemotherapy until recovered to Grade 0 or baseline, change cisplatin to carboplatin, if possible; dose reduction by 25% for other drug; if recur, stop chemotherapy
Ototoxicity	Grade 2	Dose reduction of all further doses of cisplatin by 25%
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 2, change cisplatin to carboplatin
Sensory neuropathy	Grade 2	Dose reduction for all further doses of cisplatin by 25%
	Grade 3	Stop cisplatin, change cisplatin to carboplatin
	Grade 4	Stop cisplatin/carboplatin
Other organ toxicity	Grade 2	Delay chemotherapy until ≤ Grade 1 or baseline*
	Grade 3-4	Delay chemotherapy until recovered to ≤ Grade 1 or baseline*, dose reduction of all further dose by 25%

Note: If considered in the best interest of the patient and consistent with local practice, the investigators may decide to use supportive measures / treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.

*Skin reactions, paronychia, alopecia, fatigue, nausea/vomiting which may have resolved to Grade 2 or baseline.