TITLE PAGE OF CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Open-Label, Multicenter, Prospective Clinical Study to Investigate the Efficacy and Safety of Tislelizumab (Anti-PD-1 Antibody) Combined with Chemotherapy in Patients with Brain Metastases of Non-squamous Non-small Cell Lung Cancer Who Had Not Received Prior Systemic Therapy
Protocol Identifier:	BGB-A317-2003-IIT
Phase:	2
Investigational Agent(s):	Tislelizumab
Indication:	Patients with brain metastases of non-squamous NSCLC.
Sponsor:	Sun Yat-Sen University Cancer Center
Version Number:	Version 1.2

PROTOCOL APPROVAL SHEET

Protocol Title: A Phase 2, Open-Label, Multicenter, Prospective Clinical Study to Investigate the Efficacy and Safety of Tislelizumab (Anti-PD-1 Antibody) Combined with Chemotherapy in Patients with Brain Metastases of Non-squamous Non-small Cell Lung Cancer Who Had Not Received Prior Systemic Therapy

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Sponsor: Sun Yat-Sen University Cancer Center

Signatory of Protocol/Protocol Amendment

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I Confirm That I Have Read This Protocol, I Understand It, And I Will Work According To This Protocol. I Will Also Work Consistently With The Ethical Principles That Have Their Origin In The *Declaration Of Helsink*i 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 Acceptance Of This Document Constitutes My Agreement That No Unpublished Information Contained Herein Will Be Published Or Disclosed Without Prior Written Approval From Sponsor.

I Have Read This Protocol In Its Entirety And Agree To Conduct The Study Accordingly:

Investigator's Name:_____

Investigator Title: _____

Name/Address of Center: _____

Signature of Investigator:_____ Date: _____

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SYNOPSIS

Study Title: A Phase 2, Open-Label, Multicenter, Prospective Clinical Study to Investigate the Efficacy and Safety of Tislelizumab (Anti-PD-1 Antibody) Combined with Chemotherapy in Patients with Brain Metastases of Non-squamous Non-small Cell Lung Cancer Who Had Not Received Prior Systemic Therapy
Protocol Identifier: BGB-A317-2003-IIT
Sponsor: Sun Yat-Sen University Cancer Center
Principal Investigator: Professor Li Zhang
Study Phase: 2
Indication: Patients with brain metastases of non-squamous NSCLC without prior systemic therapy
Planned Number of Patients: Approximately 35 patients
Study Centers: Approximately 8 sites
Study Objective: Primary Objective: • To assess the 1-year progression-free survival (PFS) rate of tislelizumab combined with chemotherapy (carboplatin/ pemetrexed) in patients with brain metastases of non-squamous NSCLC without prior systemic therapy. Secondary Objectives: • Objective response rate (ORR) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; • Disease control rate (DCR) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; • PFS as assessed according to RECIST v1.1; • Intracranial objective response rate (iORR), intracranial disease control rate (iDCR), and 1-year intracranial progression-free survival (PFS) rate assessed according to response assessment in neuro-oncology - brain metastases (RANO-BM). • To assess overall survival (OS); • Duration of response (DoR) as assessed according to RECIST v1.1;

- Safety profile of study treatment as assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0;
- To assess worsening of neurocognitive function;

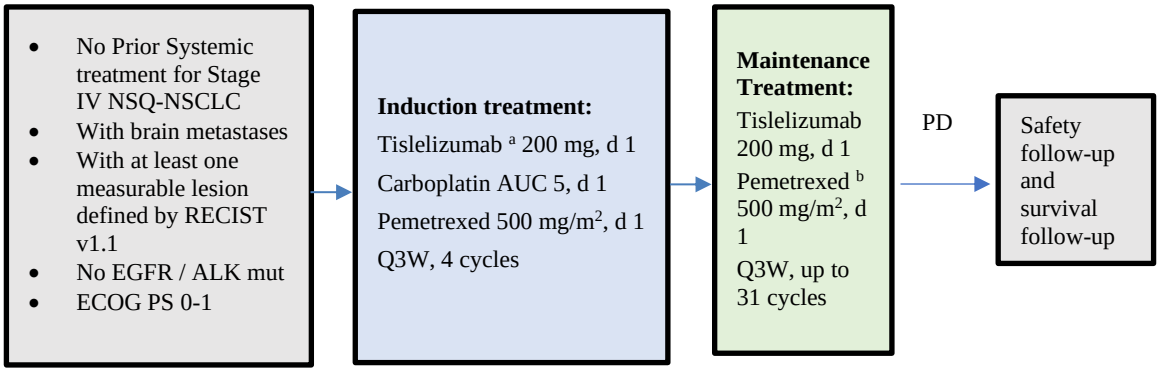
Exploratory Objectives:

- To assess PD-L1 expression, TMB and other potential predictive biomarkers and their association with efficacy and mechanisms of resistance;

Study Design:

This is a phase 2, open-label, multicenter, prospective clinical study investigating the efficacy and safety of tislelizumab combined with pemetrexed/carboplatin in patients with brain metastases of NSQ-NSCLC who had not received prior systemic therapy.

The primary endpoint will be the 1-year PFS rate.



Abbreviations: ECOG, Eastern Collaborative Oncology Group; NSQ-NSCLC, Non-squamous non-small cell lung cancer; BM(s), brain metastases; Q3W, once every 3 weeks; PD, progressive disease.

a. The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes. If well tolerated, subsequent infusions can be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of > 30 minutes would be required.
b. At the investigator's discretion, pemetrexed will be added to the maintenance phase.

During induction phase, tislelizumab + pemetrexed + carboplatin will be administered on a Q3W schedule until one of the following occurs (whichever occurs first): 1) completion of administration of 4 cycles; 2) unacceptable toxicity; or 3) documented PD per RECIST v1.1.

After completion of the induction phase, patients without documented PD will continue to receive maintenance therapy: tislelizumab with or without pemetrexed will be administered on a Q3W schedule until one of the following occurs (whichever occurs first): 1) unacceptable toxicity; 2) completion of 2 years of tislelizumab treatment 3) documented PD per RECIST v1.1.

If radiographic progressive disease is suspected by the investigator to reflect pseudoprogression regardless of the RECIST v1.1 defined PD criteria are met, the patient may continue treatment with tislelizumab until progressive disease is confirmed by repeated imaging at ≥ 4 weeks later but not exceeding 8 weeks from the date of initial documentation of progressive disease.

The following criteria must be met for patients to continue study treatment:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values);
- Stable ECOG PS ≤ 1;
- Absence of rapid PD or of progressive tumor at critical anatomical sites (e.g., cord compression) that requires urgent alternative medical intervention;
- Written informed consent form (ICF) is required from patients.

Study Assessments:

Tumor imaging at screening will be performed within 28 days before first dose of study drugs. During the study, tumor imaging assessments will be performed approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for Month 7 to Year 1, and every 12 weeks (± 7 days) from Year 2 onwards. Assessments will be performed by investigators until PD or death, whichever occurs first.

All adverse events (AEs) will be recorded during the study (AE from the time of the first dose and serious adverse events [SAEs] from the time of signing of ICF) and for up to 30 days after the last dose of study drug (including chemotherapy agents) or until the initiation of another anticancer therapy, whichever occurs first. Immune-related AEs will be reported until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy.

Study Duration:

From screening to the end of the study, the total duration of this study is expected to be 3 years, including accrual duration of 12 months.

Statistical Analysis Timepoint:

The primary endpoint 1-year PFS rate, secondary endpoints ORR, DoR, safety endpoints intracranial ORR, intracranial DCR, and 1-year intracranial PFS rate will be analyzed at 12 months after the last patient in (LPI); subsequent follow-up analyses include secondary efficacy endpoints analyses and exploratory biomarker analyses, all of which will be performed at the end of the study.

Sample Size Calculation:

Approximately 35 patients will be enrolled.

The primary endpoint of this study is the 1-year PFS rate, while the historical control of 1-year PFS rate is set at 8.6% (based on the Study KEYNOTE-189). The 1-year PFS rate

of this study is assumed at 25%, and a one-sided α of 0.05 and 80% power is used to calculate the sample size. Considering the accrual duration of 12 months and the follow-up period of 12 months, the sample size is calculated as 31 patients. Assuming a 10% dropout rate, therefore 35 patients are expected to be enrolled.

Inclusion Criteria:

Disease-related inclusion criteria:

1. Histologically confirmed metastatic (Stage IV) not amenable to curative surgery or radiotherapy, non-squamous NSCLC according to American Joint Committee on Cancer (AJCC), 8th Edition.
2. Radiographically confirmed brain metastases;
3. No prior systemic treatment for stage IV NSCLC. (Bevacizumab administered for improving radiation-induced encephaledema during irradiating intracranial lesions is not considered as systemic therapy for stage IV NSCLC)
4. Patients with asymptomatic BM or symptoms can be controlled by low dose corticosteroids (≤ 10 mg/day of prednisone or equivalent) or antiepileptics drugs;
5. Patients with previous local treatment to BMs should be stable and suitable to receive the systemic treatment;
6. ECOG PS: 0 ~ 1
7. Extracranial measurable target lesions (per RECIST v1.1)
8. Life expectancy ≥ 3 months

Have adequate hematology, clinical chemistry, and organ function as indicated by the following laboratory values (confirmed within 7 days prior to the first dose):

9. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets ≥ 100×10^9/L, hemoglobin ≥ 90 g/L.
10. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × upper limit of normal [ULN].
11. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.
12. Serum total bilirubin ≤ 1.5 × ULN (total bilirubin must be < 3 × ULN for patients with Gilbert's syndrome).
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN or AST and ALT ≤ 5 × ULN for patients with liver metastases.

General inclusion criteria:

14. Able to provide written ICF signed by patient or by his/her legally authorized representative or guardian and can understand and agree to comply with the study protocol and follow-up procedures.
15. Male or female, aged 18 ~ 75 years on the day of signing ICF.

16. Female patients of childbearing potential and non-sterile male patients must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of tislelizumab.

Exclusion Criteria:

Disease-related exclusion criteria:

1. Received prior therapies targeting PD-1, PD-L1, CTLA-4 or other immune checkpoints inhibitors.
2. Received prior systemic chemotherapy for advanced disease.
3. Have EGFR mutation or ALK gene translocation.
4. Patients with BMs that have received systemic treatment with corticosteroids (>10 mg/day of prednisone or equivalent) to relieve or prevent symptoms of BMs.
5. Patients with intracranial metastases that are amenable to local therapy.
6. Have received any approved systemic anticancer therapy or systemic immunomodulators (including but not limited to interferon, interleukin-2, and tumor necrosis factor) within 4 weeks prior to the first dose of study drug.
7. Have clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to the first dose of study drugs.
8. Active leptomeningeal metastasis.

Exclusion criteria related to study drugs:

9. History of allergic reactions to any study drugs and their excipients.
10. Creatinine clearance (Ccr) < 45 mL/min.
11. Patients with active viral hepatitis that requires treatment as judged by the investigator: a. chronic hepatitis B virus carriers with HBV DNA ≥ 500 IU/mL (2500 copies/mL) (The HBV DNA test will be performed only for patients who have a positive antibody to hepatitis B core antigen (anti-HBc antibody) test); b. patients who have positive hepatitis C virus (HCV) RNA results (The HCV RNA test will be performed only for patients testing positive for HCV antibody).
12. Active autoimmune diseases that requires systemic treatment and may impact study treatment as assessed by investigator.
13. Any condition that required extensive chronic treatment with either corticosteroids or any other immunosuppressive medications that may impact study treatment as assessed by investigator.

General exclusion criteria:

14. Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection, etc.;

1) Serious infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia;

2) Receive therapeutic oral or intravenous antibiotics within 2 weeks before first dose. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.

15. Major surgery requiring general anesthesia within 4 weeks before first dose.
16. Underlying medical conditions or alcohol or drug abuse or dependence that are to be unfavorable for the administration of study drugs or may have affected the interpretation of the results or rendered the patient at high risk from treatment complications.
17. Concurrent participation in another therapeutic clinical study.
18. Female patients who are pregnant, breastfeeding, or males and females patients planning to have child during the study.

Investigational Product, Dose, and Mode of Administration

Tislelizumab, 200mg administered by intravenous infusion once every 3 weeks.

Non-investigational Product, Dose, and Mode of Administration
Pemetrexed, 500 mg/ m^2, IV, Q3W.

Carboplatin, AUC 5, IV, Q3W

Efficacy Analyses:

The Overall Efficacy Analysis Set includes all patients who receive ≥ 1 dose of study drug, have finished tumor assessment at baseline, and ≥ 1 post-treatment tumor response assessment unless treatment is discontinued due to any clinical progressive disease or death before the first tumor assessment.

The Intracranial Efficacy Analysis Set includes all patients who receive ≥ 1 dose of study drug, have finished intracranial tumor assessment at baseline, and ≥ 1 post-treatment intracranial tumor response assessment unless treatment is discontinued due to any clinical progressive disease or death before the first tumor assessment.

Primary efficacy measurements analysis:

The primary efficacy measurement is the 1-year PFS rate. Progression-free survival (PFS) is defined as the time from first dose of study drug until first documentation of disease progression or death, whichever occurs first. Data for patients without documented PD at the time of analysis will be censored at the time of the last tumor assessment. Based on previous studies, the 1-year PFS rate of 8.6% is assumed for historical control population of this study. The 1-year PFS rate will be estimated using the Kaplan-Meier (KM) method along with corresponding two-sided 95% confidence interval (95% CI) constructed using Greenwood's formula. If the lower bound of the 95% CI for the 1-year PFS rate is higher

than 8.6%, it can be concluded that study treatment has achieved a statistically significant increase of 1-year PFS rate compared with historical control data.

Secondary efficacy measurements analyses:

Secondary efficacy measurements include ORR, PFS, iORR, iPFS, OS and DoR, etc. The time point estimates will be calculated for ORR and iORR with its precision assessed by Clopper-Pearson two-sided 95% confidence interval (CI).

The Kaplan-Meier (KM) method (Moro-Sibilot et al 2015) will be used to plot survival curves and estimate corresponding quantiles (including the median) for PFS, iPFS, OS and DOR. The two-sided 95% CIs of median for each secondary efficacy measurement will be calculated using Brookmeyer Crowley method, if applicable.

The 1-year iPFS rate will be estimated using the KM method along with corresponding 95% CI constructed using Greenwood's formula.

Safety Analysis:

The Safety Analysis Set includes all patients who receive ≥ 1 dose of tislelizumab.

Safety will be assessed by monitoring and recording of all AEs. Laboratory values (e.g., hematology, clinical chemistry and urinalysis), vital signs, electrocardiograms (ECGs), and physical examinations will be used for safety assessment. Descriptive statistics will be used to analyze all safety data in the Safety Analysis Set.

Extent of exposure to study drug will be summarized descriptively as the number of cycles received, duration of exposure and cumulative total dose received per patient.

Description of AEs will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA) terms and graded per NCI-CTCAE v5.0. A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after study drug(s) discontinuation or initiation of a new anticancer therapy, whichever occurs first. Immune-related treatment-related AEs (irAEs) will be recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. Treatment-related AEs (TRAEs) include those events considered by the investigator to be related to a study treatment or with missing assessment of the causal relationship. All TEAEs will be summarized; ≥ Grade 3 TEAEs, TEAEs leading to treatment discontinuation, dose interruption, dose reduction, or dose delay, irAEs, SAEs, deaths, and TRAEs, ≥ Grade 3 TRAEs, TRAEs leading to treatment discontinuation, dose interruption, dose reduction, or dose delay will also be summarized.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Glutamic pyruvic transaminase
AST	Glutamic oxaloacetic transaminase
AUC	Area under the plasma concentration-time curve
BM(s)	Brain metastases
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatinine kinase isoenzyme
CL	Clearance
C_{max}	Maximum concentration
CPI	Checkpoint inhibitor
CR	Complete response
CT	Computed tomography scan
DCR	Disease control rate
ddPCR	Droplet digital PCR
DoR	Duration of response
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture (system)
FDA	US 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 on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IgG	Immunoglobulin G (Including IgG1, IgG2, IgG3, and IgG4)

Abbreviation	Definition
irAE	Immune-related adverse events
IRB	Institutional review board
IRC	Independent review committee
IV	Intravenous injection
MRI	Magnetic resonance imaging
NA	Not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death-1
PD-L1	Program cell death protein ligand-1
PCR	Polymerase chain reaction
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PT	Prothrombin time
RANO-BM	Response Assessment in Neuro-oncology - Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable disease
$T_{1/2}$	Half life
TC	Tumor cells
TEAE	Treatment emergent adverse event
TPS	Tumor proportion score
ULN	Upper limit of normal range
Vd	Apparent volume of distribution

1. STUDY BACKGROUND

1.1. Non-Small Cell Lung Cancer

Lung cancer is the most common cancer in the world, with approximately 1.8 million new diagnoses and 1.59 million deaths occurred worldwide in 2012, which corresponds to the highest incidence among cancers and most common cancer-related mortality (Ferlay et al 2015). In China, there were estimated to be 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 (Molina et al 2008) and originates from the epithelial cells of the lung with the following major histological subtypes: squamous cell carcinoma, adenocarcinoma, large cell carcinoma as well as other rare histological subtypes. Lung cancers beyond the squamous cell histological subtype are collectively referred to as non-squamous NSCLC, accounting for approximately 60% of all lung cancer incidence (Howlader et al 2015).

However, prognosis of NSCLC greatly depends on the stage of cancer detected. According to the eighth edition of tumor, lymph node, and metastasis (TNM) Classification of Malignant Tumors (Goldstraw et al 2016), if NSCLC is diagnosed in its earliest stages, a cure is possible through surgery and/or chemoradiation therapy. However, approximately 70% of NSCLC patients develop advanced disease at the time of initial diagnose, i.e., commonly at stage IIIB/C or stage IV, with 5-year survival rates of 26% for patients with NSCLC stage IIIB, 13% for patients with NSCLC stage IIIC, 10% for patients with NSCLC stage IVA, and less than 1% for patients with NSCLC stage IVB.

Treatment options for advanced NSCLC include chemotherapy, targeted therapy, and the emerging immunotherapy and depend on genotyping, histology [non-squamous vs squamous cell], and performance status (PS). Although currently the advanced NSCLC is not curable, survival and prognosis can be significantly improved with appropriate treatments.

1.2. Progresses in Treating Advanced Driver Gene-Negative NSCLC

1.2.1. Platinum-Based Doublet Chemotherapy as First-line Treatment for Advanced NSCLC

In the 1990s, platinum-based doublet chemotherapy was shown to significantly extend the OS of patients with NSCLC and thus became the first-line standard of care for NSCLC. The phase 3 clinical study ECOG1594 (Schiller et al 2002) compared the efficacy of four commonly used platinum-containing doublet regimens i.e., gemcitabine + cisplatin, docetaxel + cisplatin, paclitaxel + carboplatin, and paclitaxel + cisplatin as first-line treatment for advanced NSCLC. The results showed that none of the chemotherapy regimens had significant clinical advantages over other chemotherapy regimens. The ORR was 17 ~ 22%, with a median OS = 7.4 ~ 8.1 months in the 4 treatment arms, indicating that chemotherapy reached a plateau of efficacy.

Pemetrexed is a novel antifolate antimetabolite. The phase 3 clinical study JMDB (Scagliotti et al 2008) compared the efficacy and safety of pemetrexed + cisplatin (CP) and gemcitabine + cisplatin (CG) as first-line treatment for advanced NSCLC. The results showed that in the non-squamous cell subgroup, CP regimen significantly extended OS (mOS = 11.8 m vs 10.4 m, adjusted HR = 0.81, 95% CI = 0.70 ~ 0.94), and the hematological toxicity of CP was significantly lower than the CG regimen. The phase 3 clinical study JMIL in the Chinese population (Wu et al 2014) compared efficacy and safety of pemetrexed + cisplatin (CP) and gemcitabine + cisplatin (CG) as first-line treatment for advanced non-squamous NSCLC, and the results showed that CP regimen did not have significant OS benefit over CG regimen (mOS = 17.54 m vs 15.51 m, adjusted HR = 1.03, 95% CI 0.77 ~ 1.39), the CP regimen had a favorable safety profile than CG regimen, and the incidence of treatment-related Grade 3/4 AEs was significantly reduced (43.2% vs 55.9%). A phase 3 clinical study of pemetrexed (PARAMONT) confirmed that when compared with best supportive care, pemetrexed maintenance therapy significantly extended PFS (HR = 0.62, 95% CI 0.49 to 0.79; P < .0001) (Paz-Areset al 2012) and OS (HR = 0.78; 95% CI, 0.64 to 0.96; P = .0195) (Paz-Ares et al 2013). Based on the results of Study PARAMONT, pemetrexed maintenance therapy has been recommended by the NCCN guidelines.

1.2.2. PD-1/PD-L1 Inhibitor as First-line Treatment for Driver Gene-Negative NSCLC

PD-1/PD-L1 inhibitors combined with chemotherapy have demonstrated prominent synergic effects in the first-line treatment of driver-gene wild-type NSCLC, with significantly improved ORR, extended PFS and OS, as well as favorable safety profiles. Increasing evidence suggests that the antitumor activity of chemotherapy is mediated not only through cytotoxic effects, but also through immunological effects, including reducing regulatory T cell activity, facilitating antigen exposure and enhancing cross-presentation of tumor antigens. Chemotherapy has also been shown to induce PD-L1 expression on tumor cells (Patel and Kurzrock 2015, Jin and Yoon 2016, Van Der Kraak et al 2016) therefore adding PD-1/PD-L1 inhibitors to chemotherapy may achieve better antitumor effects.

Several phase 3 clinical studies that investigated PD-1/PD-L1 inhibitors as monotherapy or investigated PD-1/PD-L1 inhibitors in combination with chemotherapy compared with platinum-based doublet chemotherapy have yielded positive results. PD-1/PD-L1 inhibitors are now becoming an important treatment approach to the first-line treatment for driver gene-negative NSCLC; currently US FDA has approved pembrolizumab and atezolizumab for this indication.

Pembrolizumab, an anti-PD-1 IgG4 antibody, is approved by US FDA as monotherapy for the first-line treatment of PD-L1-positive NSCLC, in combination with pemetrexed/platinum-based chemotherapy for the first-line treatment of non-squamous NSCLC, and in combination with nab-paclitaxel/platinum-based chemotherapy for the first-line treatment of squamous NSCLC and no PD-L1 expression screening is needed when combined with chemotherapy. Relevant clinical study data are presented in Table 1. Currently, China National Medical Products Administration (NMPA) only approved

pembrolizumab in combination with pemetrexed/platinum-based chemotherapy for the first-line treatment of non-squamous NSCLC indication.

Atezolizumab, a genetically modified anti-PD-L1 IgG1 antibody, has been approved by US FDA for use with paclitaxel + carboplatin + bevacizumab as quadruple regimen for the first-line treatment of non-squamous NSCLC. In July 2019, the European Medicines Agency (EMA) also approved atezolizumab in combination with nab-paclitaxel + carboplatin for the first-line treatment of non-squamous NSCLC. No PD-L1 expression screening is needed for all these regimens. Relevant clinical study data are presented in Table 1.

Table 1: Summary of Clinical Studies with Approved PD-1/PD-L1 Inhibitors as First-Line Treatment for Advanced NSCLC

	PD-1/PD-L1 inhibitor monotherapy as first-line treatment for advanced NSCLC		**PD-1/PD-L1 inhibitor combined with chemotherapy as first-line treatment for advanced squamous NSCLC**		**PD-1/PD-L1 inhibitor combined with chemotherapy as first-line treatment for advanced non-squamous NSCLC**					
Study	**KEYNOTE042** (Mok et al 2019)		**KEYNOTE407** (Paz-Ares et al 2018)		**KEYNOTE189** (Gandhi et al 2018)		**IMpoer150** (Socinski et al 2018)		**IMpower130** (West et al 2019)	
Number of patients	N=1274		N=559		N=616		N=692*		N=679*	
Treatment	Pembrolizumab monotherapy (n=637)	Platinum-based doublet chemotherapy regimen (n=637)	Pembrolizumab + (nab-)paclitaxel/carboplatin (n=278)	(Nab-)Paclitaxel/carboplatin (n=281)	Pembrolizumab + pemetrexed/platinum-based chemotherapy (n=410)	Pemetrexed/platinum-based chemotherapy (n=206)	Atezolizumab + paclitaxel/carboplatin + bevacizumab (n=356)	Paclitaxel/carboplatin + bevacizumab (n=336)	Atezolizumab + nab-paclitaxel/carboplatin (n=451)	Nab-paclitaxel/carboplatin (n=228)
OS (months)	16.7	12.1	15.9 (13.2-NR)	11.3 (9.5-14.8)	NR (NR-NR)	11.3 (8.7-15.1)	19.2 (17.0–23.8)	14.7 (13.3–16.9)	18.6 (16.0–21.2)	13.9 (12.0–18.7)
HR, (95% CI)	0.81 (0.71–0.93, *p* =0·0018)		0.64 (0.49–0.85, *p*<0.001)		0.49 (0.38–0.64, *p*<0.001)		0.78 (0.64–0.96, *p* = 0.02)		0.79 (0.64–0.98, *p* = 0.033)	
mPFS (month)	5.4	6.5	6.4 (6.2-8.3)	4.8 (4.3-5.7)	8.8 (7.6-9.2)	4.9 (4.7-5.5)	8.3 (7.7–9.8)	6.8 (6.0–7.1)	7 (6.2–7.3)	5.5 (4.4–5.9)
HR, (95% CI)	1.07 (0·94–1·21)		0.56 (0.45–0.70, *p* <0.001)		0.52 (0.43–0.64, *p* <0.001)		0.62 (0.52–0.74, *p* <0.001)		0.64 (0.54–0.77, *p* <0.0001)	
ORR (%)	27	27	57.9 (95% CI = 51.9-63.8)	38.4 (95% CI = 32.7-44.4)	47.6 (95% CI = 42.6–52.5)	18.9 (95% CI = 13.8-25)	63.5 (95% CI = 58.2–68.5)	48.0 (95% CI = 42.5–53.6)	49.2 (95% CI =44.5–54.0)	31.9 (95% CI = 25.8–38.4)
≥ Grade 3 TRAEs (%)	18	41	69.8	68.2	67.2	65.8	58.5	50	75	61

Abbreviations: HR, hazard ratio; mOS, median overall survival in months; mPFS, median progression-free survival in months; ORR, objective response rate (%); PD-1, programmed cell death protein-1; PD-L1, program cell death protein ligand-1; NA, not applicable; NR, not reported; TRAE, treatment related adverse event; * driver-gene wild-type patients in ITT Population.

1.3. Progresses in Treating Brain Metastases of Advanced NSCLC

Approximately 25% ~ 30% of patients have BMs at the initial diagnosis of advanced NSCLC (Wang et al 2017) and overall, the incidence of BMs in non-squamous NSCLC is higher than that of squamous type. Clinically, based on the presence or absence of symptoms of BMs, these patients are divided into asymptomatic or symptomatic patients. Approximately two-thirds of patients with BMs at initial diagnosis are patients and are only radiologically confirmed (Iuchi et al 2015).

Locoregional therapy is currently recommended as the initial treatment of patients with symptomatic BMs of NSCLC, mainly including stereotactic radiotherapy and whole brain irradiation, and surgery may be considered for selected patients with isolated intracranial lesion (Planchard et al 2019, (Ciuleanu et al 2009). Systemic therapy, such as systemic chemotherapy or targeted therapy is recommended for patients with asymptomatic BMs or stable BMs of NSCLC after locoregional therapy. Among them, targeted therapy has shown superior survival benefit over conventional chemotherapy in the first-line treatment of BMs of NSCLC harboring EGFR/ALK-sensitizing mutations (Soria et al 2018, Gadgeel et al 2018).

In contrast, standard doublet-chemotherapy regimens have limited efficacy in patients with BMs of driver-gene negative NSCLC. The FRAME study (Moro-Sibilot et al 2015) showed a median PFS of 4.0 months (95% CI: 3.0 to 5.8) and a median OS of 9.3 months (95% CI: 6.2 to 11.9) for pemetrexed plus platinum-based chemotherapy in patients with BM of non-squamous NSCLC who had not received prior systemic therapy.

In recent two years, registration clinical trials of PD-1/PD-L1 inhibitors as monotherapy or in combination with chemotherapy achieved positive results in the first-line treatment for advanced driver-gene negative NSCLC, as shown in Table 1. Although the incidence of BMs is high in advanced NSCLC, patients with untreated and/or unstable BMs, even the entire BM patient population, are largely excluded from pivotal clinical trials of immune checkpoint inhibitors. The use of glucocorticoids which may inactivate the immune response, inability of immune check point inhibitors penetrating blood brain barrier (although peripherally activated T cells can cross the blood-tumor barrier) and the risk of BM pseudoprogression may account for excluding these patients. Therefore, data available for patients with BMs of NSCLC are limited; most clinical trials have no adequate representative patients, and no stratification was performed based on the presence of BMs, and only a few trials have pre-planned BM subgroup analysis (Gandhi et al 2018).The efficacy of PD-1/PD-L1 inhibitors in treating NSCLC patients with BMs without sensitizing mutation is attracting increasing attention from academics.

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

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

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

Tislelizumab is an IgG4-variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and has very low binding affinity to complement 1q (C1q), a subunit of complement 1. *In vitro* assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn et al 2009, Zhang et al 2018).

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-dose regimens spanned from the intended human dose to 10-fold higher than the maximum of the intended human dose, and the repeated-dose regimens spanned the intended human dose to 3-fold higher than the maximum of the intended human dose. Cynomolgus monkey was the only relevant species based on target sequence homology and binding activity.

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

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

1.4.3. Clinical Pharmacology

In Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim PK analysis (cut-off date 28 August 2017) was conducted by noncompartmental methods, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, 10 mg/kg Q2W and 2.0 mg/kg, 5.0 mg/kg, 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). C_{max} and AUC increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration at steady state. Preliminary PK data from 27 patients who were administered 1 dose of 200 mg 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 (Vd) 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 With Tislelizumab

As of 10 April 2019, there are 24 ongoing studies with tislelizumab, including monotherapy and combination studies in solid tumors and hematological malignancies. Of the ongoing monotherapy studies in solid tumors, available safety and efficacy data from BGB-A317_Study_001 and BGB-A317-102 are summarized below (with a data cutoff date of 27 October 2018 and 11 May 2018).

Refer to the Tislelizumab Investigator's Brochure for more detailed information on the safety and efficacy data of tislelizumab when given as monotherapy or in combination with chemotherapy.

1.4.4.1. BGB-A317_Study_001(Data Cut-off Date 27 October 2018)

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 for the Phase 1b, and a flat dose (fixed dose) followed by a Phase 1b component to investigate efficacy in select tumor types in 9 indication-specific expansion arms including esophageal cancer (EC), gastric cancer (GC), hepatocellular cancer (HCC), and non-small cell lung cancer (NSCLC) to further evaluate safety and tolerability of tislelizumab.

The study enrolled 451 patients across 27 study centers in 5 countries. In Phase 1a of the study, 116 patients were treated and 335 patients were enrolled in Phase 1b of the study across 9 indication expansion arms. At the time of the data cutoff, there were 39 patients who remained on treatment with tislelizumab (13 patients in Phase 1a and 26 patients in Phase 1b), and 99 patients remained on study in survival follow up (31 patients in Phase 1a and 68 patients in Phase 1b), following cessation of treatment with tislelizumab.

Safety and Tolerability (Data Cutoff Date 27 October 2018)

Of the 451 total patients in the Safety Population for BGB-A317_Study_001, 259 (57.4%) experienced at least 1 treatment-emergent adverse event (TEAE) assessed as related to tislelizumab by the investigator and 38 (8.4%) experienced at least 1 ≥ Grade 3 TEAE related to tislelizumab. The most commonly occurring treatment-related TEAEs for patients treated with the tislelizumab monotherapy in BGB-A317_Study_001 were fatigue (28.2%), nausea (24.6%), decreased appetite (20.2%), diarrhea (18.2%), constipation (17.1%), abdominal pain (14.9%), vomiting (14.4%), back pain (14.2%), rash (13.5%), cough (13.7%) and dyspnoea (10.0%). The most common (≥ 1%) Grade 3 or Grade 4 TEAEs included anaemia (4.9%), pneumonia (4.4%), hypokalaemia (2.0%), diarrhea, fatigue, vomiting, and ALT increased (1.8% each); and AST increased, abdominal pain, ascites, dysphagia, and pneumonitis (1.6% each). Lastly, 26 patients (5.8%) experienced an infusion-related reaction; all were mild/moderate in severity.

Thirty-eight patients (8.4%) experienced at least 1 ≥ Grade 3 tislelizumab-related TEAE. The most common tislelizumab-related TEAEs in ≥ 3 patients included pneumonitis (1.3%), ALT increased (1.3%), AST increased (0.9%), and colitis, diarrhoea, and fatigue (0.7% each). Fatal TEAEs not due to progressive disease were reported in 15 patients (3.3%). Eight patients died within 30 days of last dose, and the reasons for death include hemoptysis, septicemia, infective mediastinitis, ischemic heart disease, pneumonia (n = 2), pneumonitis, and septic shock/disease progression. Seven patients died > 30 days after the last dose; the reasons for death were acute hepatitis, cardiac arrest, and pneumothorax (1 patient each), and unknown cause (4 patients).

Summary of Overall Response Rate

Phase 1a/1b,

Overall, the confirmed ORR was higher in Phase 1a (18.1%) than in Phase 1b (11.6%). Although CR (1.1%) was observed, PR (12.2%) was the predominant type of response. When SD was considered, the overall DCR and the overall CBR were 44.8% and 25.9%, respectively. Similarly, DCR (54.3% vs 30.2%) and CBR (41.5% vs 24.5%) were higher in phase 1a than in phase 1b.

Table 2: Tumor Response in Phase 1b of Study BGB-A317_Study_001

Cancer classification	Gastric cancer (N = 54)（N = 54）	Esophageal cancer（N = 54）	Hepatocellular cancer（N = 50）	Ovarian cancer（N = 51）	NSCLC（N = 49）	TNBC（N = 21）	CRC（N = 21）
Objective response rate (CR and PR)							
n (%)	7 (13.0)	6 (11.1)	6 (12.0)	5 (9.8)	6 (12.2)	0 (0.0)	3 (14.3)
(Exact 95% CI)	(5.37, 24.90)	(4.19, 22.63)	(4.53, 24.31)	(3.26, 21.41)	(4.63, 24.77)	(0.00, 16.11)	(3.05, 36.34)
Best overall response – confirmed, n (%)							
CR	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	7 (13.0)	5 (9.3)	6 (12.0)	5 (9.8)	6 (12.2)	0 (0.0)	3 (14.3)
SD	9 (16.7)	14 (25.9)	19 (38.0)	19 (37.3)	23 (46.9)	3 (14.3)	8 (38.1)
PD	31 (57.4)	24 (44.4)	23 (46.0)	25 (49.0)	13 (26.5)	14 (66.7)	7 (33.3)
NE	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	1 (4.8)	1 (4.8)
Missing	7 (13.0)	9 (16.7)	2 (4.0)	2 (3.9)	6 (12.2)	3 (14.3)	2 (9.5)

Abbreviations: CR, complete response; CRC, colorectal cancer; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TNBC, triple negative breast cancer.

1.4.4.2. Study BGB-A317_102 (Data Cut-off Date 1 December 2018)

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

Overall, 300 patients were enrolled in Study BGB-A317-102, including 20 patients in Phase 1 dose verification sub-study, 57 patients in Phase 1 PK sub-study, and 223 patients in Phase 2 dose expansion study. The median age was 56.5 years, 69.4% of the population was male, and 100% of patients were Asian (Chinese). Over 96% of patients had any prior anticancer treatment. The median number of prior anticancer therapy regimens was 2 (range: 0 to 11). Forty-five percent of the patients in this study had received ≥ 3 prior systemic anticancer therapies.

Safety and Tolerability

Of the 300 total patients in the Safety Population for Study BGB-A317-102, 261 (87.0%) experienced at least 1 TEAE assessed as related to tislelizumab by the investigator and 99 (33.0%) were ≥ Grade 3 in severity. The most commonly occurring (reported in ≥ 10% of patients) TEAEs related to tislelizumab were AST increased (22.3%), ALT increased (19.7%), anaemia (23.3%), blood bilirubin increased (13.3%), proteinuria (14.3%), hypothyroidism and white blood cell decreased (11.0% each), pyrexia (10.3%), and bilirubin conjugated increased (10.7%). The ≥ Grade 3 tislelizumab-related TEAEs

occurring in ≥ 2% of patients included GGT increased (4.0%), anaemia (3.0%), and AST increased (2.7%). Overall, 76 patient (25.3%) experienced at least 1 serious TEAE. The most frequently reported (in ≥ 1% of patients) serious TEAEs were pneumonia (7 patients, 2.3%), upper gastrointestinal haemorrhage and death (1.3% each). All other AEs were reported in< 1% of patients.

Summary of Overall Response Rate

Phase 1 Dose verification study

Three patients (15.0%) had a BOR of PR, 6 patients (30.0%) had a BOR of SD, and 9 patients (45.0%) had a BOR of PD. Response was unknown for 2 patients. The ORR (CR + PR) was 15% (95% CI: 3.2, 37.9). The CBR (CR + PR + SD ≥ 24 weeks) was 35% (95% CI: 15.4, 59.2), and DCR (CR + PR + SD) was 45% (95% CI: 23.1, 68.5).

PK Sub-study

One patient (ID: 18104) (1.8%) had a BOR of CR, 9 patients (15.8%) had a BOR of PR, 11 patients (19.3%) had a BOR of SD and 25 patients (43.9%) had a BOR of PD. Response was not evaluable for 2 patients and unknown for 9 patients. The ORR (CR + PR) was 17.5% (95% CI: 8.7, 29.9). The CBR (CR + PR + SD ≥ 24 weeks) was 26.3% (95% CI: 15.5, 39.7), and DCR (CR + PR + SD) was 36.8% (95% CI: 24.4, 50.7).

Phase 2 Study

Thirty two patients (14.3%) had a BOR of PR, 74 patients (33.2%) had a BOR of SD, and 81 patients (36.3%) had a BOR of PD. Response was unknown for 36 patients. The ORR (CR + PR) was 14.3% (95% CI: 10.0, 19.6). The CBR (CR + PR + SD ≥ 24 weeks) was 30.9% (95% CI: 24.9, 37.5), and DCR (CR + PR + SD) was 47.5% (95% CI: 40.8, 54.3).

Table 3: Tumor Response in Phase 2 of Study BGB-A317-102

Cancer classification	MSI-H/ dMMRa (N = 16)	Esophageal cancer (N = 26)	Gastric cancer (N = 24)	Hepatocellular cancer (N = 18)	Melanoma (N = 34)
Objective response rate (CR and PR)					
n (%)	3 (18.8)	2 (7.7)	4 (16.7)	3 (16.7)	5 (14.7)
(Exact 95% CI)	(4.0, 45.6)	(0.9, 25.1)	(4.7, 37.4)	(3.6, 41.4)	(5.0, 31.1)
Best overall response – confirmed, n (%)					
CR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	3 (13.8)	2 (7.7)	4 (16.7)	3 (16.7)	5 (14.7)
SD	5 (31.3)	7 (26.9)	3 (12.5)	7 (38.9)	8 (23.5)
PD	6 (37.5)	13 (50.0)	9 (37.5)	8 (44.4)	17 (50.0)
NE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	2 (12.5)	4 (15.4)	8 (33.3)	0 (0.0)	6 4 (11.8)

Abbreviations: CR, complete response; MSI-H/dMMR, microsatellite instability- high/mismatch repair deficient-; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Cancers with centrally confirmed MSI-H/dMMR. One patient was included both in MSI-H/dMMR and GC cohorts

1.4.4.3. Immune-Related Reactions

Immune-related adverse events were reported in 23.1% of patients treated in BGB-A317_Study_001 and 16.0% of patients treated in Study BGB-A317-102. The irAEs that occurred in at least 2% of patient in the overall population are detailed in Table 4 below. The sponsor adjudicated these irAEs across both studies to harmonize the definition of irAE in accordance to published guidelines for irAEs.

Table 4: Immune-related TEAEs of Tislelizumab as Adjudicated by Investigator

	BGB-A317_Study_001 [a] N = 451 n (%)	Study BGB-A317-102 [b] N = 300 n (%)
Thyroid dysfunction	39 (8.6)	25 (8.3)
Skin reactions	39 (8.6)	9 (3.0)
Pneumonitis	12 (2.7)	7 (2.3)
Hepatitis	10 (2.2)	5 (1.7)
Colitis	9 (2.0)	0

[a] As of October 27, 2018. [b] As of December 1, 2018

Of these irAEs, immune-mediated skin reactions were reported more frequently in study BGB-A317_Study_001 in the overall population as compared to study BGB-A317-102. Most of these events were Grade 1 or 2 in severity, Grade 3 events were less frequently reported.

In study BGB-A317_Study_001, the potential irAEs assessed as ≥ Grade 3 were: Grade 3 pneumonitis and ALT increased in 6 patients (1.3%) each, diarrhea and colitis in 3 patients (0.7%) each, GGT increased and hyperglycemia in 2 patients (0.4%) each. All other potential irAEs assessed as ≥ Grade 3 were events in single patients, including a Grade 4 event of diabetic ketoacidosis in a patient with adenoid cystic carcinoma, and 2 patients with Grade 5 events of acute hepatitis in a patient with HCC and pneumonitis in a patient with NSCLC.

In Study BGB-A317-102, the only Grade 4 event reported was a single case of an adverse skin reaction. There were no deaths due to irAE in Study BGB-A317-102.

1.4.4.4. Study BGB-A317-206 (Data Cut-off Date 15 October 2018)

Study BGB-A317-206 is a multi-arm Phase 2 study, consisting of safety run-in and dose-extension phases, assessed tislelizumab in combination with platinum-based chemotherapy (by tumor histology) (4 arms) as a potential first-line treatment for Chinese patients with lung cancer. All patients received tislelizumab at 200mg once every 3 weeks in combination with 4 to 6 cycles of platinum-based doublet chemotherapy until disease progression.

A total of 54 patients were enrolled into the study; 37 of those were patients with NSCLC (3 arms). Of the 3 enrolled NSCLC arms, 32 patients (86.5%) remained on study as of 15 October 2018; 17 patients (45.9%) were still receiving tislelizumab treatment, and 15 patients (40.5%) were in follow-up. The median duration of exposure to tislelizumab and chemotherapy for the 3 arms was 28 to 39 weeks and 16.5 to 27.5 weeks, respectively. The majority of patients (89.2%) received 4 or more cycles of combination treatment without disease progression.

Preliminary safety

In the safety analysis of the total population, 39 patients (72.2%) experienced ≥ Grade 3 TRAEs, of which 7 patients (13.0%) experienced ≥ Grade 3 tislelizumab-related TEAEs. The most common Grade ≥3 TRAE was decreased neutrophil count(48.1%). Fourteen patients (25.9%) experienced at least one treatment-emergent SAE, and SAEs reported in ≥ 2 of the patients included anemia, thrombocytopenia, pneumonitis, and platelet count decreased. One patient experienced ≥ Grade 3 irAE of myocarditis/myositis with a fatal outcome. With the exception of a single Grade 5 event, other AEs were manageable and reversible by tislelizumab interruption or discontinuation (7 patients, 13%) and by appropriate treatment as clinically indicated.

Preliminary efficacy

- In the ITT population, confirmed responses were observed in 36 (66.7%) patients. Additionally, 13 patients (24.1%) had a BOR of SD. Confirmed ORRs were 43%, 80%, 66.7%, and 76.5% in the non-squamous cell lung cancer cohort (16 patients), squamous cell lung cancer cohort A (15 patients), squamous cell lung cancer cohort B (6 patients), and small cell lung cancer cohort (17 patients), respectively.
- The median time to first response was 12 weeks, 5.9 weeks, 5.7 weeks, and 6.0 weeks in the non-squamous cell lung cancer cohort, squamous cell lung cancer cohort A, squamous cell lung cancer cohort B, and small cell lung cancer cohort, respectively, and the median PFS was 9.0 months, 7.0 months, NR, and 6.9 months, respectively; the median OS in the small cell lung cancer cohort was 15.6 months, and the OS in the remaining cohorts was not mature (data cutoff date 25 February 2019).

A Phase 3 confirmatory study that investigates the efficacy and safety of tislelizumab combined with platinum-based chemotherapy and pemetrexed versus platinum-based chemotherapy and pemetrexed alone as first-line treatment for driver-gene wild-type non-squamous NSCLC is initiated based on favorable safety and therapeutic activity shown in Phase 2 trials, and the enrollment has been completed.

1.5. Study Rationale

1.5.1. Rationale for PD-1 Antibodies Combined with Chemotherapy as First-line Treatment for Brain Metastases of NSCLC

Basic researches suggest that activated effector T cells could enter the brain through pia mater vessels, postcapillary venules and tight junctions between neighboring choroid plexus endothelial cells, reach the intracranial tumor site, and attack tumor cells locally (Ratnam et al 2019). Compression of the surrounding tissues and blood vessels by intracranial tumors can also cause ischemic necrosis and edema, causing pathological dysplasia of cerebral capillaries, sparse intercellular space of endothelial cells, and enhanced pinocytosis, which may further lead to increased barrier permeability; under such condition, endothelial cells are damaged, tight junction structures are lost and basement

membrane are damaged, therefore lymphocytes and leukocytes and plasma components including antibodies can also enter the brain parenchyma (Iwasaki et al 2017)

Benefits in the brain metastatic population have been observed in multiple studies of anti-PD-1/PD-L1 monotherapy as subsequent-line treatment for NSCLC. In Study Checkmat057, OS was generally comparable between BM patients treated with nivolumab and those treated with docetaxel (HR = 1.04) (Borghaei et al 2015), while in the OAK study, the OS was significantly higher in those treated with atezolizumab than those treated with docetaxel alone (HR = 0.54) (Rittmeyer et al 2017). Besides, a real-world study demonstrated that the 1-year OS rate was generally comparable (43% vs 48%) between patients with BMs of NSCLC who had received nivolumab monotherapy as subsequent-line therapy (N = 409) and the overall NSCLC population (N = 1588) (Crinò et al 2019). These results suggest that patients with BMs of NSCLC can benefit from anti-PD-1/PD-L1 inhibitors therapy.

Anti-PD-1/PD-L1 inhibitors combined with chemotherapy have demonstrated prominent synergic effects in the first-line treatment of driver-gene negative NSCLC, with significantly improved ORR, extended PFS and OS, as well as favorable safety profile (see Table 1). It is suggested that the addition of PD-1/PD-L1 inhibitors to chemotherapy may achieve better antitumor effects. A post-hoc analysis of patients with asymptomatic or treated stable brain metastases (N = 108) in Study KEYNOT189 showed a 1-year PFS rate = 31.6%, mPFS = 4.7 months, and mOS = 19.3 months for pembrolizumab combined with pemetrexed plus platinum-based chemotherapy (Garassino et al 2019 AACR). These results suggest that patients with BMs of NSCLC can benefit from anti-PD-1/PD-L1 inhibitors in combination with chemotherapy as first-line treatments.

1.5.2. Rationale for Selection of Tislelizumab in Combination With Chemotherapy

High levels of FcγR-expressing myeloid derived cells (e.g., M2 macrophage, myeloid-derived suppressor cell [MDSC]) in tumor tissues are associated with a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated antibody-dependent cellular cytotoxicity (ADCC) or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T-cells (Gul and van Egmond 2015, Makarova-Rusher et al 2015, Prieto et al 2015, Beers et al 2016). As a no-to low-FcγR-binding agent (thus causing minimal ADCC/ADCP effect), tislelizumab is expected to potentially show superior efficacy and lower toxicity in clinical practice. Based on preliminary data with tislelizumab monotherapy in a Phase 1/2 studies (BGB-A317_Study_001/102), tislelizumab appears comparable to other anti-PD-1 CPIs in terms of safety and preliminary activity in patients with advanced solid tumors. In addition, the ongoing Phase 2 study (BGB-A317-206), which evaluates the combination of tislelizumab and various standard of care chemotherapies as first-line treatment for lung cancer, showed promising efficacy and similar safety signals compared to other CPIs in combination with chemotherapy. A Phase 3 clinical study (BGB-A317-304) evaluating tislelizumab in combination with chemotherapy as first-line treatment for driver gene-negative advanced non-squamous NSCLC is ongoing. This study is designed to investigate tislelizumab combined with chemotherapy in patients with brain metastases of non-squamous NSCLC.

1.5.3. Rationale for Selection of Tislelizumab in Combination with Pemetrexed/Carboplatin

The phase 3 clinical study ECOG1594 (Schiller et al 2002)showed comparable efficacy among four commonly used platinum-containing doublet regimens i.e., gemcitabine + cisplatin (GC), docetaxel + cisplatin (DC), paclitaxel + carboplatin (PCb), and paclitaxel + cisplatin （PC） as first-line treatment for advanced NSCLC, only PCb regimen had a favorable safety profile. Pemetrexed is a novel antifolate antimetabolite. The phase 3 clinical study JMDB (Scagliotti et al 2008) compared the efficacy and safety of pemetrexed + cisplatin (CP) and gemcitabine + cisplatin (CG) as first-line treatment for advanced NSCLC. The results showed that in the non-squamous cell subgroup, CP regimen significantly extended OS (mOS = 11.8 m vs 10.4 m, adjusted HR = 0.81, 95% CI = 0.70 ~ 0.94), and the hematological toxicity of CP was significantly lower than the CG regimen. In addition, pemetrexed/carboplatin has been selected as the chemotherapy regimen in multiple Phase 3 studies investigating PD-1/PD-L1 inhibitors in combination with chemotherapy, such as Study KEYNOTE189, IMpower132, CheckMate-227, etc. In summary, pemetrexed/carboplatin is also selected as the chemotherapy regimen in this study.

1.5.4. Rationale for Selection of Tislelizumab in Combination with Pemetrexed as Maintenance Therapy

A phase 3 clinical study of pemetrexed (PARAMONT) confirmed that when compared with best supportive care, pemetrexed maintenance therapy significantly extended PFS (HR = 0.62, 95% CI 0.49 to 0.79; P < .0001) (Paz-Ares et al 2012) and OS (HR = 0.78; 95% CI, 0.64 to 0.96; P = .0195) (Paz-Ares et al 2013) Based on the results of PARAMONT study, pemetrexed maintenance therapy has been recommended by the NCCN guidelines. In this study, tislelizumab + pemetrexed is selected as maintenance therapy for patients who has not experienced PD after 4 cycles of tislelizumab in combination with pemetrexed/carboplatin.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objective

2.1.1. Primary Objective

- To assess the 1-year progression-free survival (PFS) rate of tislelizumab combined with chemotherapy (carboplatin/ pemetrexed) in patients with brain metastases of non-squamous NSCLC without prior systemic therapy.

2.1.2. Secondary Objectives

- Objective response rate (ORR) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
- Disease control rate (DCR) as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;

- PFS as assessed according to RECIST v1.1;
- Intracranial objective response rate (iORR), intracranial disease control rate (iDCR), and 1-year intracranial progression-free survival (PFS) rate assessed according to response assessment in neuro-oncology - brain metastases (RANO-BM).
- To assess overall survival (OS);
- Duration of response (DoR) as assessed according to RECIST v1.1;
- Safety profile of study treatment as assessed according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0;
- To assess worsening of neurocognitive function.

Exploratory Objectives:

2.1.3. Exploratory Objectives

- To assess PD-L1 expression, TMB and other potential predictive biomarkers and their association with efficacy and mechanisms of resistance;

2.2. Study Endpoints

2.2.1. Primary Endpoint

- One-year PFS rate - PFS is defined as the time from first dose to the first objectively documented disease progression, or death from any cause, whichever occurs first, and the 1-year PFS rate will be estimated by the Kaplan-Meier (KM) method and assessed by the investigator according to RECIST v1.1 in an efficacy analysis set.

2.2.2. Secondary Endpoints

- ORR as assessed by the investigator – the proportion of patients who had complete response (CR) or partial response (PR) as assessed by the investigator per RECIST v1.1 in an overall efficacy analysis set.
- DCR as assessed by the investigator – 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 in an overall efficacy analysis set.
- PFS – PFS is defined as the time from first dose to the first objectively documented disease progression, or death from any cause, whichever occurs first, as assessed by the investigator per RECIST v1.1 in an overall efficacy analysis set.
- The 1-year iPFS rate - The 1-year iPFS rate is defined as the proportion of patients who have no intracranial disease progression/death after ≥ 1 years of treatment with the protocol-defined regimens in an efficacy analysis set. Intracranial progressive disease will be assessed by the investigator per RANO-

BM in an efficacy analysis set. Intracranial progressive disease is defined as new intracranial lesions and/or a 20% increase in the sum of long diameter of measurable intracranial lesions at baseline and/or significant progression of non-measurable intracranial lesions at baseline and/or worsening of clinical status.

- Intracranial ORR as assessed by the investigator – the proportion of patients who had intracranial complete response (CR) or partial response (PR) as assessed by the investigator per RANO-BM in intracranial efficacy analysis set.
- Intracranial DCR as assessed by the investigator – the proportion of patients who had intracranial complete response (CR), partial response (PR) or stable disease (SD) as assessed by the investigator per RANO-BM in intracranial efficacy analysis set.
- OS – OS is defined as the time from the date of first dose to the date of death due to any cause in an efficacy analysis set.
- Worsening of neurocognitive function as assessed according to the Hopkins Verbal Learning Test–Revised (HVLT-R) scale.
- DoR - DoR is defined as 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 investigator per RECIST v1.1 in all patients with documented objective responses.
- Incidence and severity of treatment-emergent adverse events (TEAEs) graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), v5.0.

2.2.3. Exploratory Endpoints

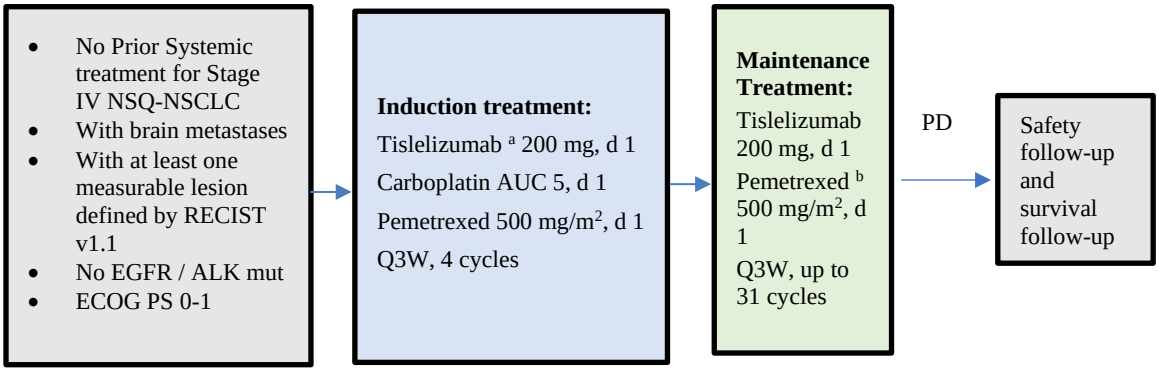
- To assess PD-L1 expression, TMB and other potential predictive biomarkers and their association with efficacy and mechanisms of resistance;

3. STUDY DESIGN

3.1. Summary of Study Design

This is a phase 2, open-label, multicenter, prospective cohort clinical study investigating the efficacy and safety of tislelizumab combined with pemetrexed/carboplatin in patients with brain metastases of non-squamous NSCLC patients who had not received prior systemic therapy. The primary endpoint will be the 1-year PFS rate.

Figure 1: Study Schema



Abbreviations: NSQ-NSCLC, non-squamous non-small cell lung cancer; BMs, brain metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; AUC, area under the time-concentration curve; Q3W, every three weeks; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

a. The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes. If well tolerated, subsequent infusions can be administered over 30 minutes. After tislelizumab infusion, patients will be further monitored for at least 1 hour during Cycles 1 and 2. From Cycle 3 onward, a post-infusion monitoring period of > 30 minutes would be required.

b. At the investigator's discretion, pemetrexed will be added to the maintenance phase.

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose. Patients who agree to participate will sign the ICF before 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.

3.3. Treatment Period

After completing all screening activities, patients confirmed to be eligible will be enrolled. During induction phase, tislelizumab + pemetrexed + carboplatin will be administered on a Q3W schedule until one of the following occurs (whichever occurs first): 1) completion of administration of 4 cycles; 2) unacceptable toxicity; or 3) documented PD per RECIST v1.1.

After completion of the induction phase, patients without documented PD will continue to receive maintenance therapy: tislelizumab with or without pemetrexed will be administered on a Q3W schedule until one of the following occurs (whichever occurs first): 1)

unacceptable toxicity; 2) completion of 2 years of tislelizumab treatment 3) documented PD per RECIST v1.1.

If radiographic progressive disease is suspected by the investigator to reflect pseudoprogression regardless of the RECIST v1.1 defined PD criteria are met, the patient may continue treatment with tislelizumab until progressive disease is confirmed by repeated imaging at ≥ 4 weeks later but not exceeding 8 weeks from the date of initial documentation of progressive disease.

The following criteria must be met for patients to continue study treatment:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values).
- Stable ECOG PS ≤ 1;
- Absence of rapid PD or of progressive tumor at critical anatomical sites (eg cord compression) that requires urgent alternative medical intervention.
- Written ICF is obtained from individual patients.

3.4. Safety Follow-up Visit

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit 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 irAEs and concomitant medications (i.e., associated with an irAE or is a new anticancer therapy) if appropriate at 60 days (± 14 days), and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. If patients report a suspected irAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.3.

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 occurs 30 days (± 7 days) after the last study treatment. Patients who discontinue from study treatment before disease progression will need to undergo tumor assessments as outlined in Section 7.5.

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

3.5. Survival Follow-up Visit

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, study completion by the sponsor.

3.6. Discontinuation From Study Treatment (s) or From the Study

3.6.1. Patient Discontinuation From Study Treatment

The patient may discontinue study treatment for any reason and at any time. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression, should be followed for assessments of antitumor efficacy (Section 7.5), safety (Section 7.4) 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 study treatment for reasons that include but are not limited to the following:

- Disease progression assessed per RECIST v1.1
- Pregnancy
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she is to continue the study treatment
- Prohibited concomitant medications are used, refer to Section6.2.2.
- Patient noncompliance to study treatment

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

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

- Patient withdrawal of consent
- Death
- Loss to follow-up
- Patient has completed all study assessments

3.7. End of Study

The accrual period is approximately 12 months, and the analysis of the primary endpoint 1-year PFS rate analysis is expected to be performed after 12 months of last patient enrolled in the total population. Survival follow-up Visit will continue for approximately 24 months after the last patient in or until all patients are dead, whichever occurs first. After this point, the study will be closed and no data will be collected.

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 significantly lower than expected.

4. STUDY POPULATION

The investigator must keep records (e.g., patient screening logs) of patients who have entered the study for screening. This information is to indicate that there will be no deviations during the selection of patients.

4.1. Inclusion Criteria

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

Disease-related inclusion criteria:

1. Histologically confirmed metastatic (Stage IV) not amenable to curative surgery or radiotherapy, non-squamous NSCLC according to American Joint Committee on Cancer (AJCC), 8th Edition.
2. Radiographically confirmed brain metastases;
3. No prior systemic treatment for stage IV NSCLC. (Bevacizumab administered for improving radiation-induced encephaledema during irradiating intracranial lesions is not considered as systemic therapy for stage IV NSCLC)
4. Patients with asymptomatic BM or symptoms can be controlled by low dose corticosteroids (≤ 10 mg/day of prednisone or equivalent) or antiepileptics drugs;
5. Patients with previous local treatment to BMs should be stable and suitable to receive the systemic treatment;
6. ECOG PS: 0 ~ 1
7. Extracranial measurable target lesions (per RECIST v1.1)
8. Life expectancy ≥ 3 months

Have adequate hematology, clinical chemistry and organ function as indicated by the following laboratory values (confirmed within 7 days prior to the first dose):

9. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelets ≥ 100 × 10^9/L, hemoglobin ≥ 90 g/L.
10. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × upper limit of normal [ULN]
11. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN
12. Serum total bilirubin ≤ 1.5 × ULN (total bilirubin must be < 3 × ULN for patients with Gilbert's syndrome).
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN or AST and ALT ≤ 5 × ULN for patients with liver metastases.

General inclusion criteria:

14. Able to provide written ICF signed by patient or by his/her legally authorized representative or guardian and can understand and agree to comply with the study protocol and follow-up procedures.

15. Male or female, aged 18 ~ 75 years on the day of signing ICF.
16. Female patients of childbearing potential and non-sterile male patients must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of tislelizumab.

4.2. Exclusion Criteria

Disease-related exclusion criteria:

1. Received prior therapies targeting PD-1, PD-L1, CTLA-4 or other immune checkpoints inhibitors.
2. Received prior systemic chemotherapy for advanced disease. (Bevacizumab administered for improving radiation-induced encephaledema during irradiating intracranial lesions is not considered as systemic therapy for stage IV NSCLC)
3. Have EGFR mutation or ALK gene translocation.
4. Patients with BMs that have received systemic treatment with corticosteroids (>10 mg/day of prednisone or equivalent) to relieve or prevent symptoms of BM.
5. Patients with intracranial metastases that are amenable to local therapy.
6. Have received any approved systemic anticancer therapy or systemic immunomodulators (including but not limited to interferon, interleukin-2, and tumor necrosis factor) within 4 weeks prior to the first dose of study drug.
7. Clinically uncontrolled pleural effusion or ascites that requires pleurocentesis or abdominal tapping for drainage within 2 weeks prior to the first dose of study drugs.
8. Active leptomeningeal metastasis.

Exclusion criteria related to study drugs:

9. History of allergic reactions to any study drugs and their excipients.
10. Creatinine clearance (Ccr) < 45 mL/min.
11. Patients with active viral hepatitis that requires treatment as judged by the investigator: a. chronic hepatitis B virus carriers with HBV DNA ≥ 500 IU/mL (2500 copies/mL) (The HBV DNA test will be performed only for patients who have a positive antibody to hepatitis B core antigen (anti-HBc antibody) test); b. patients who have positive hepatitis C virus (HCV) RNA results (The HCV RNA test will be performed only for patients testing positive for HCV antibody).
12. Active autoimmune diseases that requires systemic treatment and may impact study treatment as assessed by investigator.
13. Any condition that required extensive chronic treatment with either corticosteroids or any other immunosuppressive medications that may impact study treatment as assessed by investigator.

General exclusion criteria:

14. Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection, etc.;

    1) Serious infections within 4 weeks before first dose, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia;

    2) Receive therapeutic oral or intravenous antibiotics within 2 weeks before first dose. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.

15. Major surgery requiring general anesthesia within 4 weeks before first dose.
16. Underlying medical conditions or alcohol or drug abuse or dependence that are to be unfavorable for the administration of study drugs or may have affected the interpretation of the results or rendered the patient at high risk from treatment complications.
17. Concurrent participation in another therapeutic clinical study.
18. Female patients who are pregnant, breastfeeding, or males and females patients planning to have child during the study.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for intravenous 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 study drug must be kept at the temperature condition specified on the label.

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

5.1.2. Chemotherapy Agents

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

For further details, see the manufacturer's prescribing information for each chemotherapy agent.

5.2. Dosage, Administration, and Compliance

Dosing schedules for all investigational agents are provided in Table 5. All patients will be monitored continuously for AEs. Treatment modifications (e.g., dose delay, reduction, interruption or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.4.

For each cycle, tislelizumab will be administered before chemotherapy drugs; pemetrexed administration will be performed before carboplatin during the induction phase.

Table 5: Selection and Timing of Dose for Each Patient

Study Drug	Dose	Frequency of administration	Route of administration	Duration of treatment
Tislelizumab	200 mg	Day 1 of each cycle	Intravenous	Induction + Maintenance, see Section 3.3
Carboplatin	AUC 5	Day 1 of each cycle	Intravenous	Induction, see Section 3.3
Pemetrexed	500 mg/m^2	Day 1 of each cycle	Intravenous	Induction + Maintenance, see Section 3.3
Abbreviation: AUC, area under the plasma or serum concentration-time curve.				

5.2.1. Tislelizumab

Tislelizumab 200mg 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.

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

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (see Section 6.2).

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any AEs. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of tislelizumab therapy. Guidelines for dose modification, treatment interruption, or discontinuation are provided in Section 5.4, and specifically for the management of irAE and infusion-related reactions are provided in detail in Section 8.8 and Appendix 4.

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

5.2.2. Chemotherapy

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes on Day 1 of each cycle for 4 cycles; then pemetrexed maintenance treatment will be continued, at the investigator's discretion, until disease progression or unacceptable toxicity. In addition, all patients should receive the appropriate corticosteroid premedications as per the local approved label. Patients should receive antiemetics, hormone, folic acid, vitamin B16 and IV hydration for carboplatin/pemetrexed treatments according to the local standard of care and manufacturer's instruction.

During the induction phase, carboplatin AUC 5 will be administered as an IV infusion over 15 minutes on Day 1 of each cycle for 4 cycles immediately after pemetrexed.

In special situations (e.g., when the administration is delayed due to management of AEs or in the case of an infusion-related reaction due to tislelizumab), administration of the subsequent chemotherapy drugs can be delayed to the second day of each cycle.

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

When clinically feasible, premedication with steroids should be limited due to their immunomodulatory effects. In addition, in the event of chemotherapeutic agent-related skin rash, topical steroid use is recommended as front-line treatment unless IV steroids are considered clinically necessary.

Other prophylactic medications should be administered according to standard of care practices. All medications will be documented in the appropriate concomitant medication eCRF.

Patients will be monitored continuously for AEs and will be instructed to notify their physician immediately for any 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 5.4.

5.3. Investigational Agents Accountability

Tislelizumab is the study drug (IMP) required for this study.

Accurate records of all IMPs received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log.

5.4. Dose Delay, Interruption, or Modifications

Every effort should be made to administer tislelizumab and chemotherapy on the same day according to the planned dose and schedule (see Appendix 1), and as 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.

Dose interruptions are permitted in the case of medical/surgical events or personal reasons not related to study treatment (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients are required to be placed back on study therapy within 3 weeks of the scheduled interruption, unless discussed with the sponsor. The reason for the interruption of treatment should be recorded.

Reasons for dose modifications or holds, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. The severity of AEs will be graded according to the NCI-CTCAE v5.0 grading system.

5.4.1. General Guidance Regarding Dose Modifications

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

- Dose modifications for chemotherapy should be performed per prescribing information and per local practice according to the treating physician's clinical judgment (please see Section 5.4.3).
- No dose modification is needed for tislelizumab, and dose delay is allowed as defined in Section 5.4.2.
- For any AEs already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels

it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases 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 solely due to 1 component of the study treatment (i.e., tislelizumab, carboplatin, or pemetrexed), other components may be administered if there is no contraindication.
- The tislelizumab and chemotherapy infusions ideally remain synchronized.

5.4.2. Dose Interruption or Delay for Tislelizumab

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

Dose delays or interruptions < 12 weeks will be permitted. The patient should resume tislelizumab treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is the more severe) at the next scheduled cycle. If a patient is unable to resume tislelizumab within 12 weeks after the last dose, then the patient should be discontinued from treatment.

If a dose for a planned dosing cycle (e.g., Cycle 3 Day 1) is delayed for tislelizumab for ≤ 10 days, tislelizumab will 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 (i.e., Cycle 4, Day 1).

Dose modification related to irAEs and infusion-related reactions are described in Appendix 4and Section 8.8.1 respectively.

5.4.3. Dose Modification for Chemotherapy

Dose modification for chemotherapy will be performed per prescribing information and per local practice according to the treating physician's clinical judgment.

Chemotherapeutic agent-related toxicities must be resolved to baseline or Grade 0 or ~ 1 prior to administering the next dose, except for alopecia or Grade 2 fatigue. Only 1 dose reduction is permitted for carboplatin, a maximum of 2 dose reductions are permitted for pemetrexed. Once the dose has been decreased, it should remain reduced for all subsequent administrations. If additional reductions are required, that chemotherapeutic agent must be discontinued. There are no dose escalations in this study. Chemotherapy administration may be delayed up to 21 days, if the reason for the delay is toxicity/adverse event. All subsequent chemotherapy doses should be rescheduled according to the last chemotherapy dose administration date.

If a dose for a planned dosing cycle (e.g., Cycle 3 Day 1) is delayed for chemotherapy for ≤ 10 days due to chemotherapy-related toxicities, chemotherapy will be administered (on the same day with tislelizumab, if applicable). All subsequent chemotherapy doses will be

rescheduled according to the last chemotherapy dose administration date. If the delay is > 10 days but ≤ 21 days, the patient should skip the chemotherapy, and tislelizumab and chemotherapy will be administered on Day 1 of the next planned cycle (i.e., Cycle 4, Day 1).

Recommendations regarding dose modifications for certain chemotherapy-related toxicity and discontinuation of chemotherapy are detailed in Appendix 5.

6. PRIOR AND CONCOMITANT THERAPIES

6.1. Prior Therapies

According to inclusion criteria, patients with brain metastases (asymptomatic untreated or previously radiotherapy-treated stable disease) of stage IV non-squamous NSCLC who had not received prior systemic therapy will be enrolled in the study (Section 4.1). All prior cancer related treatments, treatments for underlying active medical conditions, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient ≤ 30 days before first dose must be recorded in the appropriate eCRF.

6.2. Concomitant Therapies

6.2.1. Permitted Concomitant Medications

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (e.g., antiemetics and antidiarrheals) and in a patient's interest are allowed.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 4) 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 treatment (e.g., patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Bisphosphonates are allowed for bone metastases if initiated before enrollment and at a stable dose.

Palliative 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.

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.

Additionally, palliative radiation or other focally ablative therapy for other nontarget sites of the disease is permitted if the investigator determines that it is clinically indicated. The

definition of clinically significant is entrusted to the judgment of the investigator. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the therapies in order to rule out progression of disease. It is not required to withhold study treatments during palliative radiotherapy.

6.2.2. Prohibited or Restricted Concomitant Medications

The following medications are prohibited or restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Extensive chronic systemic corticosteroids (except to treat a drug-related AE)
- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese herbal medicine and Chinese patent medicines] for the treatment of cancer) is not allowed; radiation therapy is not allowed for extracranial lesions, except for palliative radiation therapy described in Section 6.2.1.
- Live vaccines within 28 days before treatment and 60 days following the last dose of study drug(s).
- Herbal remedies with immune-stimulating properties (e.g., mistletoe extract) or that were known to potentially interfere with liver or other major organ functions (e.g., 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. If ibuprofen cannot be avoided, it should not be administered within 2 days before and after administration of pemetrexed, as concomitant administration of ibuprofen may be associated with increased toxicity of pemetrexed (including myelosuppression, gastrointestinal toxicity, and renal toxicity).

At the time of study initiation, the patient received medications to treat concomitant diseases or symptoms under the guidance of the physician, and record the drug name, start and stop date, dosage and reason for administration on the CRF. During the study, the investigator should assess the patient's concomitant diseases or symptoms at each visit, solicit patients for new diseases or symptoms, and record the drug name, start and stop date, dosage and reason for administration of all concomitant medications on the CRF. In addition, any diagnostic, therapeutic, or surgical procedure to be performed during the study should be recorded, and the date of the procedure, indication, procedure, and all clinical findings should be recorded.

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.

The major route of elimination of carboplatin is renal excretion. The renal effects of nephrotoxic compounds could be potentiated by carboplatin.

Ibuprofen has been shown to increase pemetrexed exposure and poses a risk in patients with mild/moderate renal impairment. Hence, ibuprofen should be used with caution 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.

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

7.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose. Patients who agree to participate will sign the ICF before undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator will 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 first dose may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this Section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5), and Biomarkers (Section 7.6).

7.1.1. Demographic Data and Medical History

Demographic data will include age and/or date of birth, sex, and ethnicity.

Medical history includes any history of clinically significant disease, surgery, cancer history, reproductive history, history of alcohol consumption and tobacco (i.e., former, current, or never); and all medications (e.g., prescription drugs, over-the-counter drugs, Chinese herbal medicine) used by the patient within 30 days before the first dose of study drug.

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.

7.1.2. Contraception Requirements

Childbearing potential is defined as the physiological ability to become pregnant. Female patients of childbearing potential and nonsterile males are required to take contraceptive measures. Refer to Appendix 8for contraception guidelines and definitions of "women of childbearing potential" and "women of no childbearing potential.

7.1.3. Informed Consent Forms and Screening Log

Voluntary, written, ICF for participation in the study must be obtained before performing any study-specific procedures. ICFs for enrolled patients and for patients who are screened but failure to be enrolled will be maintained at the study site.

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

7.2. Enrollment

7.2.1. Confirming Eligibility

The investigator will assess the eligibility of each patient. All results from the screening procedures 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.

After the patient is screened, the investigator will determine whether the patient is eligible for enrollment.

7.2.2. Patient Numbering

After obtaining informed consent, study site personnel will assign a unique patient number to a potential study patient.

7.3. Tislelizumab Dispensation

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

7.4. Safety Assessments

7.4.1. Vital Signs

Vital signs include the measurements of body temperature (℃), 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.

7.4.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted including evaluation of 1) head and neck: head, eyes, ears, nose, throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory, 6) gastrointestinal; and 7) neurological systems. Any abnormality identified at baseline 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 (see Appendix 4).

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 the Adverse Event eCRF. Refer to Section 8.3 and Section 8.4 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group (ECOG) Performance Status

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

7.4.4. Laboratory Safety Tests

Laboratory safety tests will be performed by a local study site laboratory. Hematology, blood chemistry, coagulation, CK/CK-MB (creatine kinase, creatine kinase isozymes) will be tested within 7 days before the first dose, and will be reassessed before any subsequent dosing, other assessments are specified as follows

1. Hematology (including red blood cell count [RBC], hemoglobin, hematocrit, white blood cell count [WBC] with differential [neutrophils], and platelet count)
2. Serum chemistry (glucose, urea nitrogen, creatinine, sodium, potassium, magnesium, chloride, calcium, phosphorus, direct bilirubin, total bilirubin, ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total protein, albumin)
3. Coagulation parameters (including international normalized ratio, prothrombin time, and activated partial thromboplastin time)
4. CK/CK-MB test (creatine kinase, creatine kinase-muscle/brain)
5. Routine urinalysis (including but not limited to specific gravity, pH, glucose, protein, ketones) must be performed within 7 days prior to the first dose and as clinically indicated during the study.

6. Urine pregnancy test must be performed within 7 days prior to the first dose in the female patient of childbearing potential and a blood pregnancy test is required to confirm if the investigator suspects that the patient may become pregnant during the study.
7. Thyroid function test (thyroid stimulating hormone [TSH], free T3, free T4) must be performed at screening and as clinically indicated during the study.
8. T-cell subset testing is performed as clinically indicated.

7.4.5. Pulmonary function Test

Pulmonary function tests including spirometry and assessment of diffusion capacity are to be performed for all patients at screening to assist patient eligibility determination, and as clinically indicated during the study treatment.

7.4.6. Electrocardiograms

Electrocardiograms (ECGs) are to be performed for all patients at screening and as clinically indicated during the study.

7.4.7. Adverse Events

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

All AE, including SAEs, will be collected as described in Section 8.3.

7.5. Tumor and Response Evaluation

Baseline tumor imaging at screening will be performed within 28 days before first dose of study drugs. During the study, tumor imaging assessments will be performed approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for Month 7 to Year 1, every 12 weeks (± 7 days) from Year 2 onwards. All measurable and evaluable lesions will be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation based on RECIST v1.1. Whenever possible, the same radiographic procedure used to assess disease sites at screening are required to be used throughout the study.

1. Screening assessments and each subsequent assessment of the tumor must include computed tomography (CT) scans of the chest, preferably with contrast.
2. Screening assessments and each subsequent assessment of the tumor must also include CT scans of the upper abdomen, preferably with contrast.
3. Screening assessments and each subsequent assessment of the tumor must include brain MRI for all patients unless contraindicated, then a CT of head may suffice.
4. Bone scans (technetium-99m) or positron emission computed tomography (PET) should be performed at screening if clinically indicated. Subsequent assessments are to be implemented if clinically indicated.

5. CT scans or B-ultrasound of the neck or extremities are also to be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.

Patient who discontinues study treatment early for reasons other than disease progression (e.g., toxicity) will continue to undergo tumor assessments following the original plan until the patient starts subsequent anticancer therapy, experiences PD, withdraws consent, 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.

7.6. Biomarkers

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

Tumor tissue samples (8 or more unstained slides) must be sent to central laboratory for central IHC assessment of PD-L1 expression. In addition to PD-L1 expression, tissue samples will also be used to measure other predicative biomarkers correlated to response, such as TMB, using immunohistochemistry (IHC) and testing of tumor associated genes based on a next-generation sequencing platform, covering 400 + tumor associated genes, and to explore their associations with response.

7.7. Visit Window

All visits must be performed within ± 3 days of the scheduled date (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. Review of laboratory results are required 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 for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from day 1 of Cycle 1.

7.8. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include disease-related constitutional symptoms, vital signs and focused physical examinations, ECOG PS, AE review, concomitant medications and procedures review; radiographic assessments, and hematology and chemistry laboratory assessments. The date, reason for an unscheduled visit and results must be recorded in the eCRF.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of AEs and SAEs that meet the criteria in this protocol.

8.1. Risks Associated With Study Drug

8.1.1. Risks Associated With Tislelizumab

Tislelizumab has been approved as monotherapy for the treatment of relapsed or refractory classical Hodgkin lymphoma, but other indications are still under study, with limited number of patients being dosed, therefore the effects of tislelizumab on humans are being observed. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data regarding other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, this type of therapy may increase the risk of irAEs or induce/ exacerbate autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.8.3.

Although most irAEs observed with anti-PD-1/PD-L1 treatments 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 4.

8.1.2. Risks Associated With Carboplatin and Pemetrexed

For NSCLC patients who are treated with carboplatin/pemetrexed in a first-line setting, frequently occurring (> 5%) Grade 3 or 4 drug-related toxicities are neutropenia, thrombocytopenia , anemia, fatigue, and peripheral neuralgia.

Please refer to Table 6 below for the reported toxicities of the respective chemotherapeutic agents. Investigators shall refer to the prescribing information for further details.

Table 6: Commonly and Specific Reported Toxicity of the Chemotherapeutic Agents

Drug	Common Toxicity	Specific Toxicity
Carboplatin	Myelodepression with leukopenia, thrombocytopenia and anemia; infectious complications; nausea/vomiting and other gastrointestinal toxicity; hepatic impairment; fatigue; anorexia; constipation	Ototoxicity and peripheral neuropathies
Pemetrexed		Nephrotoxicity; skin rash

8.2. Adverse Event

8.2.1. Definition

8.2.1.1. Adverse Event

An adverse event is defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not

considered related to the medicinal product. An adverse event could, therefore, has been any unfavorable and unintended sign, an abnormal test result (e.g., abnormal laboratory values, ECG) or disease (new or exacerbated) temporally associated with the use of an investigational product.

8.2.1.2. 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 is at risk of death at the time of the AE. It does not refer to an event that hypothetically might have caused death if it had been more severe.

- Requires hospitalization or prolongation of existing hospitalization.

Note: In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that will 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 (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.
- Is a medically significant event (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a preexisting 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.

8.3. Recording Adverse Events

8.3.1. Identifying Adverse Events

The investigator or designee will ask patients 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?

8.3.2. Adverse Event Reporting Period

All adverse events (AEs) will be recorded during the study (AE from the time of the first dose and serious adverse events [SAEs] from the time of signing of ICF) and for up to 30 days after the last dose of study drug (including chemotherapy) or until the initiation of another anticancer therapy, whichever occurs first. Immune-related AEs will be reported until 90 days after the last dose of tislelizumab regardless of whether or not the patient starts a new anticancer therapy. See Appendix 1.

8.3.3. Recording Adverse Events

All AEs should be recorded on the eCRF, and the AE description should include start/stop date, whether it constitutes a SAE, actions taken (study treatment modifications, other treatments and related examinations), and the outcome. The investigator is responsible for causality assessment.

8.3.4. Assessment of Adverse Events

The investigator will evaluate the severity for each AE and SAE reported during the study and assess and grade them according to NCI-CTCAE v5.0.

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

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

8.3.5. 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, and other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated.

The causality of each AE should be assessed and classified by the investigator as “related” or “not related”. An adverse event is considered related if there is “a reasonable possibility”

that the adverse event may have been caused by the study drug (i.e., there are facts, evidence, or arguments to suggest possible causation).

8.4. Reporting Serious Adverse Events

Any serious adverse event must be reported by the investigator or site personnel to the sponsor and the delegated contract research organization (CRO) and BeiGene within 24 hours of awareness and report to regulatory authorities and IRBs/IECs in accordance with local regulatory requirements. For incomplete SAE report, the investigator shall perform adequate investigations to obtain follow-up information.

8.5. Recording and Reporting 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 the 30 days after the last dose of chemotherapy, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor and BeiGene to facilitate outcome follow-up.

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

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

8.6. Recording Disease Progression

If it is clear that any event is due to progressive disease, the term “disease progression” should not be reported as an adverse event term. Instead, the symptoms, signs that result from disease progression should be reported as the AE term(s).

8.7. Recording 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 AE (e.g., “death,” “death of unknown cause,” or “death unexplained”). The disease diagnosis shall be updated for the cause of death once it is clear.

8.8. Management of AE of Special Interest

As a routine precaution, after the infusion of tislelizumab on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for ≥ 60 minutes afterward in an area with resuscitation equipment and emergency agents. If no infusion-related adverse reactions occur in the first two cycles , from Cycle 3 onward, at least 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.

8.8.1. Infusion-Related Reactions

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

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 7.

Table 7: 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 (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions have resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

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

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and premedication must be administered. 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 (e.g., diphenhydramine or equivalent), antipyretic (e.g., 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 (e.g., diphenhydramine or equivalent) and an antipyretic (e.g., 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 intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

8.8.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK). Patients are 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, 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 a monitor immediately and the ICU should be alerted for possible transfer if needed.

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

8.8.3. Immune-Related Adverse Events

The immune-related AEs are of special interest in this study. If the events listed below or similar events occur (Table 8), the investigator should exclude alternative explanations (e.g., concomitant medications, infectious disease or metabolic diseases, toxin, disease progression or other neoplastic causes) with appropriate diagnostic tests, which may include but is not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the irAE indicator on the eCRF AE page should be checked. A list

of potential irAEs is shown below in Table 8. All conditions similar to those listed should be evaluated in patients receiving tislelizumab to determine whether they are irAEs.

Table 8: 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 syndrome
Skin (severe-rare)	Full-thickness necrolysis syndrome/Stevens-Johnson syndrome
Gastrointestinal	Colitis (diarrhea with abdominal pain or endoscopic/radiographic evidence); diarrhea; pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	Thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, e.g., fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	Pneumonitis/diffuse alveolitis
Eye	Episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	Arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis, meningoencephalitis; myositis
Blood	Anemia; leukopenia; thrombocytopenia
Renal	Interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	Pericarditis; myocarditis; heart failure

Refer to Appendix 4 or the ESMO and ASCO Clinical Practice Guidelines for diagnostic assessment and management of irAEs (Brahmer et al 2018, Haanen et al 2018).

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 will be permanently discontinued from treatment.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

After finalization of the study protocol, a statistical analysis plan will be prepared by statisticians in consultation with the principal investigator. A general description of the statistical methods planned for the data analysis in this study is provided in the following subsections. Additional details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Analysis

9.1.1. Analysis Sets

- The Safety Analysis Set includes all patients who receive ≥ 1 of tislelizumab.
- The Overall Efficacy Analysis Set includes all patients who receive ≥ 1 dose of study drug, have finished tumor assessment at baseline, and ≥ 1 post-treatment tumor response assessment unless treatment is discontinued due to any clinical progressive disease or death before the first tumor assessment.
- The Intracranial Efficacy Analysis Set includes all patients who receive ≥ 1 dose of study drug, have finished intracranial tumor assessment at baseline, and ≥ 1 post-treatment intracranial tumor response assessment unless treatment is discontinued due to any clinical progressive disease or death before the first tumor assessment.

9.1.2. Baseline and Demographics

Demographic and other baseline characteristics will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs; categorical variables include histology; PD-L1 expression in tumor cells, disease stage, sex, ECOG PS, ethnicity, smoking and metastatic sites, etc.

9.2. Efficacy Analyses

All efficacy analyses will be performed in the Efficacy Analysis Set.

9.2.1. Primary Efficacy Measurement Analysis

One-year progression-free survival rate (1-year PFS rate): Progression-free survival (PFS) is defined as the time from first dose of study drug until first documentation of disease progression as assessed by the investigator per RECIST v1.1 or death, whichever occurs first. 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. Based on previous studies, the 1-year PFS rate of 8.6% is assumed for historical control population of this study. The 1-year PFS rate will be estimated using the Kaplan-Meier (KM) method along with corresponding two-sided 95% confidence interval (95% CI) constructed using Greenwood's formula. If the lower bound of the 95% CI for the 1-year PFS rate is higher than 8.6%, it can be concluded that study treatment has achieved a statistically significant increase of 1-year PFS rate compared with historical control data.

9.2.2. Secondary Efficacy Measurements Analyses

Objective Response Rate (ORR): ORR is defined as the proportion of patients achieving a best overall response (BOR) of CR or PR, as determined according to the RECIST v1.1.

Disease Control Rate (DCR): DCR is defined as the proportion of patients achieving a best overall response (BOR) of CR, PR or SD as determined according to the RECIST v1.1.

Intracranial ORR: iORR is defined as the proportion of patients who had intracranial complete response (CR) or partial response (PR) as assessed by the investigator per RANO-BM in intracranial efficacy analysis set.

Intracranial DCR: iDCR is defined as the proportion of patients who had intracranial complete response (CR), partial response (PR) or stable disease (SD) as assessed by the investigator per RANO-BM in intracranial efficacy analysis set.

In analysis, the time point estimates will be calculated for ORR, iORR and iDCR with its precision assessed by Clopper-Pearson two-sided 95% confidence interval (CI).

Progression-free survival (PFS): PFS is defined as the time from first dose of study drug until first documentation of disease progression as assessed by the investigator per RECIST v1.1 or death, whichever occurs first. Data for patients without documented PD at the time of analysis will be censored at the time of the last tumor assessment.

Overall survival (OS): OS is defined as time from the first dose of study drug to the date of death due to any cause. For patients who are not reported as having died at the time of analysis, OS will be censored at the date the patients were last known to be alive.

Duration of response (DoR): DoR is defined as the time from the first occurrence of a documented objective response to the time of relapse or death from any cause, whichever occurs first. Data for patients without documented PD at the time of analysis will be censored at the time of the last valid assessment.

In the analysis, the Kaplan-Meier (KM) method (Moro-Sibilot et al 2015) will be used to plot survival curves and estimate corresponding quantiles (including the median) for PFS, PFS2, OS and DoR. The two-sided 95% CIs of median for each measurement will be calculated using Brookmeyer Crowley method, if applicable.

The 1-year iPFS rate: The iPFS is defined as the time from first dose to the first objectively documented intracranial disease progression, or death from any cause, whichever occurs first. The 1-year iPFS rate is defined as the proportion of patients who have no intracranial disease progression/death after ≥ 1 years of treatment with the protocol-defined regimens in an intracranial efficacy analysis set.

The 1-year iPFS rate will be estimated by KM method and corresponding 95% CI will be calculated by using Greenwood's formula

Exploratory Analysis

To explore PD-L1 expression, tumor mutation burden (TMB), and other potential predictive biomarkers and their association with clinical efficacy of tislelizumab plus chemotherapy and mechanisms of resistance.

9.3. Safety Analyses

The Safety Analysis Set includes all patients who received ≥ 1 dose of study drug. Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE v5.0. Laboratory values (e.g., hematology, clinical chemistry and urinalysis), vital signs,

electrocardiograms (ECGs), and physical examinations will be used for safety assessment. 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 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 (milligrams), dose intensity, 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 study drug. Frequency of the above dose adjustments and discontinuation will be summarized by category.

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

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA (Version 22.1, 20.0 or higher) by lowest level term, preferred term (PT), and primary system organ class (SOC). A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug(s) and up to 30 days after study drug(s) discontinuation or initiation of a new anticancer therapy, whichever occurs first. Immune-related treatment-related AEs (irAEs) will be recorded up to 90 days after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy. Only those AEs that are treatment emergent will be included in summary tables of TEAEs.

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

9.3.3. Laboratory Analyses

Clinical laboratory (e.g., 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 are included in the clinical study report (CSR) for this protocol. Descriptive summary statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for the laboratory

parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded by 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 (e.g., glucose, potassium, sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital signs parameters (temperature, pulse, and blood pressure) and changes from baseline will be presented by visit for each visit. Vital signs will be listed by patient and visit.

9.4. Sample Size Calculation

The primary endpoint of this study is the 1-year PFS rate, while the historical control of 1-year PFS rate is set at 8.6% (based on the Study KEYNOTE-189). The 1-year PFS rate of this study is assumed at 25%, and a one-sided α of 0.05 and 80% power to calculate the sample size. Considering the accrual duration of 12 months and the follow-up period of 12 months, the sample size is calculated as 31 patients. Assuming a 10% dropout rate, therefore 35 patients are expected to be enrolled.

9.5. Statistical Analysis Timepoint

The primary endpoint (1-year PFS rate), secondary endpoints (ORR, DOR), safety endpoints and exploratory endpoint (1-year intracranial PFS rate) will be analyzed at 12 months after the last patient in (LPI); subsequent follow-up analyses include secondary efficacy endpoints analyses and exploratory biomarker analyses, all of which will be performed at the end of the study.

10. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

10.1. Monitoring

In accordance with International Council for Harmonization (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 during these monitoring visits are resolved.

10.2. Audits and Inspections

The investigator should be aware that, upon formal notification, the original records of the study are to be prepared and made available to the appropriate qualified person or his/her designee, or to inspectors of the health authorities. Reconciliation of data in the eCRF must be directly verified against the original records.

11. DATA MANAGEMENT

11.1. Electronic Case Report Form (eCRF)

Electronic case report form (eCRF) will be used in this study. For each screened patient (who has signed informed consent), the eCRF must be completed and signed by the principal investigator or by authorized study personnel. The investigator must ensure the accuracy and completeness of all data.

11.2. Database Queries and Responses

The electronic data capture (EDC) system can automatically issue queries regarding date, inclusion/exclusion criteria, drop-out, missing values while entering data into system. Data manager can manually issue queries to data point in EDC system. To address queries to data points, investigator can either respond online or provide written response and signature to a query form, which will be downloaded by medical monitor and re-uploaded to EDC by a clinical research associate. The offline query forms are to be properly maintained at each study site. For queries from EDC, the investigator should provide responses as soon as possible, and data queries may be reissued if necessary.

11.3. Data Verification and Database Lock

After all data queries in the EDC are resolved, “clean” data will be exported and made available to statisticians, while the Statistical Analysis Plan (SAP) is concurrently finalized. The database will be locked once the investigator provides the electronic signature in EDC and statistical analysis plan is finalized, then the statistical analysis will be performed as indicated in SAP.

12. ETHICS/PROTECTION OF HUMAN PATIENTS

12.1. Ethical Standard

This study will be conducted by the principal investigator and the study site in full compliance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will comply with the

requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

12.2. 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. Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

12.2.1. 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 must be obtained by the investigator 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 (e.g., a change in 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 their willingness to remain in the study.

12.3. Informed Consent

The patient should be provided with the primary information of the study and ICFs. Before the start of the study, the study personnel must provide the patient with the ICFs approved in writing by EC and all other written information. The EC approval and the approved patient information sheet/informed consent form must be archived in the study file. Informed consent is required prior to performing any study-specific procedures.

12.4. Patient and Data Confidentiality

All records regarding patient identifiers will be kept confidential and will not be made publicly available to the extent permitted by relevant laws and/or regulations. Only study personnel, such as the investigator and the study nurse know patient identity. Electronic Case Report Form (eCRF) does not include patients' names. Only the patient number and initials will be recorded in the eCRF. If other documents (such as pathology report) include patient's name, the name must be redacted on the copies. The computerized study reports

must comply with local data protection laws. The patient's identity will also be kept confidential when publishing study results. The investigator will maintain a record that can identify patients.

12.5. Publication of Study Data and Protection of Commercially Confidential Information

The results of this study may be published or reported at scientific seminars or conferences, and if such publication is foreseeable, each investigator agrees to submit all manuscripts or abstracts to the sponsor for review prior to submission. This allows the sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator. Based on standard publishing and ethics guidelines, the data pooled from multi-centers rather than single center are recommended for publication. In this condition, a coordinating investigator will be appointed after mutual agreement.

12.6. Study Agreement

The principal investigator at each site must comply with all the terms, conditions, and responsibilities stipulated in the study agreement. For the ownership of intellectual property rights and related matters, the provisions of the "Investigator Initiated Trial Agreement" should be followed if there are conflicts between the study agreements.

12.7. Study Termination

If the sponsor decides to discontinue or suspend the study, a written document with a detailed justification is required to be submitted to the principal investigator, the co-investigator, and the management of the study site. The principal investigator and co-investigators must immediately notify the patients of the above decision in this study, administer appropriate treatment, take appropriate measures to ensure the safety and well-being of patients, and document the treatments and actions in the source documents.

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APPENDIX 1: STUDY PROCEDURES

Assessment	Screening[1]		Treatment cycles			Safety follow-up[3]	Survival follow-up[4]
			Cycles 1 to 4 (every 21 days)	Cycle 5 onwards (every 21 days)	End-of-treatment visit[2]		
Days (window)	**-28 to -7**	**-7 to -1**	**1(± 3)**	**1 (± 3)**	**0 ~ 7**	**30 ± 7 days after last dose**	**Every 3 months**
Informed Consent	X						
Inclusion/exclusion criteria		X					
Demographic/medical history/prior medications[5]	X						
Vital signs/height and weight[6]		X	X	X	X	X	
Physical examination[7]		X	X	X	X	X	
ECOG PS		X	X	X	X	X	
ECG[8]	X		As clinically indicated				
AE[9]	X		X	X	X	X	X[10]
Concomitant medications	X		X	X	X	X	
Hematology[10]		X	X	X	X[2]	X	
Serum chemistry[10]		X	X	X	X[2]	X	
Coagulation parameters[10]		X	X	X	X[2]	X	

Assessment	**Screening[1]**		**Treatment cycles**			**Safety follow-up[3]**	**Survival follow-up[4]**
			Cycles 1 to 4 (every 21 days)	**Cycle 5 onwards (every 21 days)**	**End-of-treatment visit[2]**		
Days (window)	**-28 to -7**	**-7 to -1**	**1(± 3)**	**1 (± 3)**	**0 ~ 7**	**30 ± 7 days after last dose**	**Every 3 months**
Total CK and CK-MB[10]		X	X	X	X[2]	X	
Urinalysis[10]		X	As clinically indicated				
Pregnancy test[11]		X	As clinically indicated				
Thyroid function[12]	X		As clinically indicated				
T-cell population test[12]	As clinical indicated		As clinically indicated				
HBV/HCV tests[13]	X		As clinically indicated				
Pulmonary function test[14]	X		As clinically indicated				
Tumor assessment[15]	X		X	X	X[2]		
Tissue/blood sample collection[16]	X		X (optional at recurrence)				
Tislelizumab administration[17]			X	X			
Carboplatin administration[18]			X				
Pemetrexed administration[19]			X	X			
Neurocognitive function assessment[20]	X		X	X	X	X	X (optional)
Survival status							X

Abbreviations: AE, adverse event; AUC, area under the plasma or serum concentration-time curve; CK, creatinine kinase; CK-MB, creatine kinase cardiac muscle isoenzyme; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; IEC, Independent Ethics Committee; irAE, immune-related adverse event; IRB, Institutional Review Board; IRC, Independent Review Committee; IRT, interactive response technology; IV, intravenous; MRI, magnetic resonance imaging; ^{18}F-NaF PET, 18F-sodium fluoride position emission tomography; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; 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 before obtaining informed consent and within 28 days before the first dose of study drug may be used for screening assessments rather than repeating such tests.
2. The End of Treatment Visit is conducted when the investigator determines that tislelizumab or chemotherapy will no longer be used. If routine laboratory tests (e.g., hematology, serum chemistry) were 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.
3. The Safety Follow-up Visit is required to be conducted 30 days (± 7 days) after the last dose of tislelizumab and/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 termination by sponsor, whichever occurs first. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.
5. Including history of treatment for the primary diagnosis, including prior medications, locoregional therapy and surgical treatment. Radiographic studies performed prior to study entry may be collected for review by the Investigator.
6. Vital signs collected on study include temperature, pulse rate, and blood pressure. Height should only be measured and recorded during screening.
7. 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.

8. The ECG recordings will be obtained during screening and as clinically indicated at other timepoints during subsequent visits. Patients should be resting for ≥ 10 minutes prior to each ECG measurement.
9. The AEs and laboratory abnormalities will be graded per NCI-CTCAE v5.0. All adverse events will also be evaluated for seriousness. After informed consent has been signed, but prior to the administration of the study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of relationship to the study drug, will be evaluated and recorded until either 30 days after last dose of study treatment (including chemotherapy) or initiation of new anticancer therapy, whichever occurs first. Telephone contacts with patients should be conducted to assess irAEs and concomitant medications (i.e., associated with an irAE or is a new anticancer therapy) if appropriate at 60 days (± 14 days), and 90 days (± 14 days) after the last dose of tislelizumab, regardless of whether the patient starts a new anticancer therapy.
10. Laboratory assessments on hematology, blood chemistry, coagulation, total CK and CK-MB, and urinalysis will be conducted at each site, of which certain elements will be collected as specified in Section 7.4.4. Hematology, blood chemistry, coagulation, total CK and CK-MB will be tested within 7 days before first dose, and will be reassessed before subsequent dosing; urinalysis will be performed at Screening for baseline measurement and will be performed as clinically indicated during the study.
11. Urine 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 first dose. A blood pregnancy test is required to confirm if the investigator suspects that the patient may become pregnant during the study.
12. Testing and analysis of thyroid function (FT3, FT4, and TSH) will be performed by laboratories of each study site at Screening for baseline measurement and will be performed as clinically indicated during the study.
13. Testing will be performed by the laboratories of each study site at Screening and include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). These tests will be performed as clinically indicated during the study.
14. Pulmonary function tests including spirometry and assessment of diffusion capacity are to be performed for all patients at screening to assist patient eligibility determination, and as clinically indicated during the study treatment.
15. Radiological images captured before obtaining written informed consent and ≤ 28 days before first dose of study drug may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. A chest scan (CT scan), abdominal scan (CT scan or B-ultrasound), and brain MRI (CT scan if MRI is contraindicated) must be included at the Screening Visit and each subsequent assessment, and a bone scan or PET is required at the Screening

Visit and subsequent visits if clinically indicated. Whenever possible, the same radiographic procedure used to assess disease sites at screening are required to be used throughout the study.

Baseline tumor imaging at screening will be performed within 28 days before first dose of the study drug. During the study, tumor imaging assessments will be performed approximately every 6 weeks (± 7 days) for the first 6 months, every 9 weeks (± 7 days) for Month 7 to Year 1, every 12 weeks (± 7 days) from Year 2 onwards. Tumor assessments will be performed by the investigator, are not impacted by dose delay, and will continue until disease progression (per RICIST v1.1 criteria), withdrawal of consent, or death, whichever occurs first.

16. Patients must be able to provide archival/fresh tumor tissues (FFPE blocks or approximately at least 5 freshly cut unstained FFPE slides) and blood samples for biomarker analysis to assess the biomarker PD-L1 expression and for testing of tumor associated genes based on a next-generation sequencing platform to assess TMB, etc.
17. Tislelizumab will be administered intravenously for Q3W. The initial infusion (Cycle 1, Day 1) will be delivered for over 60 minutes, and then can be administered for over 30 minutes for subsequent infusions if well tolerated. Patients must be monitored for 60 minutes 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 after 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.
18. Carboplatin will be administered for 4 cycles of induction therapy. Refer to Section 5.2.2 for detail dose and schedule. Carboplatin will be administered at the dose of AUC 5, on Day 1 of each cycle.
19. Pemetrexed will be administered intravenously for 4 cycles of induction and maintenance therapy. Refer to Section 5.2.2 for detail dose and schedule. Pemetrexed will be administered at the dose of 500 mg/m^2, on Day 1 of each cycle.
20. The Hopkins Verbal Learning Test-Revised (HVLT-R) scale is used for neurocognitive assessment, see Appendix 7.

APPENDIX 2: ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 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	Death.

As published by 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.

APPENDIX 3: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) V1.1 AND RESPONSE ASSESSMENT IN NEURO-ONCOLOGY - BRAIN METASTASES (RANO-BM)

The text below is obtained from the following reference:

- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer.2009;45:228-247.
- Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol. 2015 Jun;16(6):e270-8.

Definition

Tumor response and disease progression in this study will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) (Version 1.1) and the Response Assessment in Neuro-oncology - Brain Metastases (RANO-BM) (PD of intracranial lesions will be evaluated by RANO-BM criteria). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST v1.1 and RANO-BM criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Measurable Disease

Tumor lesions: must be accurately measured in ≥ 1 dimension (longest diameter) with a minimum size of:

- 10 mm by CT and MRI (no less than double the slice thickness and a minimum of 10 mm).Assumes a scan slice thickness no greater than 5 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 computed tomography (CT) scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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 that 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 that is reported as being 20 mm by 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 a 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 nontarget lesions and should also be recorded at baseline. Measurements are not required. 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 (e.g., "multiple enlarged pelvic lymph nodes" 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. An imaging-based evaluation should always be done rather than a clinical examination, unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., 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 study.

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

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor response is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence after 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 (PSA) response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies 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 (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the

actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that 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 was the opinion of the radiologist that the lesion had likely disappeared, the measurement was 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 nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement 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 nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).

- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of 1 or more new lesions is also considered progression).

- Non-CR/Non-PD: Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The

designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept 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 nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase in 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 it 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 Lesion(s) Present

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: i.e., 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 preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study 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 scan ordered that reveals metastases. The patient's brain metastases are considered evidence of PD even if he or 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 a truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of 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 best overall response is the best response recorded from the start of the study drug treatment until the EOT 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 best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study 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 best overall response is determined once all the data for the patient are known. Best response determination in trials where confirmation of complete or partial response **IS NOT** required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be the 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 stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered non-evaluable.

Target Lesions	**Nontarget Lesions**	**New lesion(s) present**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE

Target Lesions	Nontarget Lesions	New lesion(s) present	Overall Response
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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

In studies where confirmation of response is required, repeated "not evaluable (NE)" timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of the response and progression. For example, in most studies 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 un-evaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine-needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to 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 a false positive CR because of limitations of FDG-PET and biopsy resolution/sensitivity.

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

Confirmatory Measurement/Duration of Response

Confirmation

In nonrandomized studies 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, i.e., in randomized studies (Phase 2 or 3) or studies 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 study 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 stable disease, measurements must have met the stable disease 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 the first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

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

Duration of Stable Disease

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

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

Response Assessment in Neuro-oncology - Brain Metastases RANO-BM

Proposed RANO-BM criteria

Similar to RECIST 1.1, definitions for radiographical response will be based on unidimensional measurements.

Definitions

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≤1.5 mm apart with 0 mm skip). Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline. Measurement of a tumour around a cyst or surgical cavity is a particularly difficult challenge. Generally, such lesions should be considered non-measurable unless there is a nodular component that measures 10 mm or more in longest diameter and 5 mm or more in the perpendicular plane. The cystic or surgical cavity should not be measured for the determination of a response (figure 1). Non-measurable disease includes all other lesions, including lesions with longest dimension less than 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease. We recognise that many patients with brain metastases present with small sub-centimetre lesions and that some centres routinely perform MRI imaging with 3 mm slice thickness or less. We have discussed whether the lower size limit of a measurable lesion could be reduced to 5 mm or even less. However, in view of concerns about reproducibility and interpretation of changes in small lesions, the overall consensus was to maintain consistency with RECIST 1.1. Patients with non-measurable disease can still be included in trials where response is not the primary endpoint (e.g., in trials with progression-free survival, overall survival, or other primary endpoints). For studies in which CNS objective response is the primary endpoint, we generally recommend a cutoff of 10 mm to limit the study to measurable disease. For investigators who choose to lower the minimum size limit of measurable disease to 5 mm, we strongly recommend MRI imaging with 1.5 mm slice thickness or less. Complete response and unequivocal progressive disease can probably be interpreted even with lesions as small as 5 mm. However, measurement of small changes, such as the minimum 20% increase in longest diameter to determine progressive disease or the minimum 30% decrease in longest diameter to determine partial response, might not be robust or reproducible. With the intrinsic uncertainty of measurements of small lesions, any lesion less than 10 mm in longest diameter should be regarded as unchanged from baseline unless there is a minimum 3 mm change in the measured longest diameter.

The decision to include patients with multiple lesions with a sum diameter of 10 mm or more but of which the largest lesion measures less than 10 mm should be taken with caution if objective response is the primary endpoint. If such patients are included, response should be assessed using the sum of the longest diameters of the lesions, and the response criteria should be clearly delineated in the protocol. Thin-Section MRI imaging with 1.5 mm or thinner slice thickness would be necessary in this setting .

Methods of measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Consistent use of imaging techniques across all imaging timepoints is important to ensure that the assessment of interval appearance, disappearance of lesions, or change in size is not affected by scan parameters such as

slice thickness. Use of thin Section imaging (appendix) is particularly important for the assessment of lesions less than 10 mm in longest diameter or small changes in lesion size, or both.

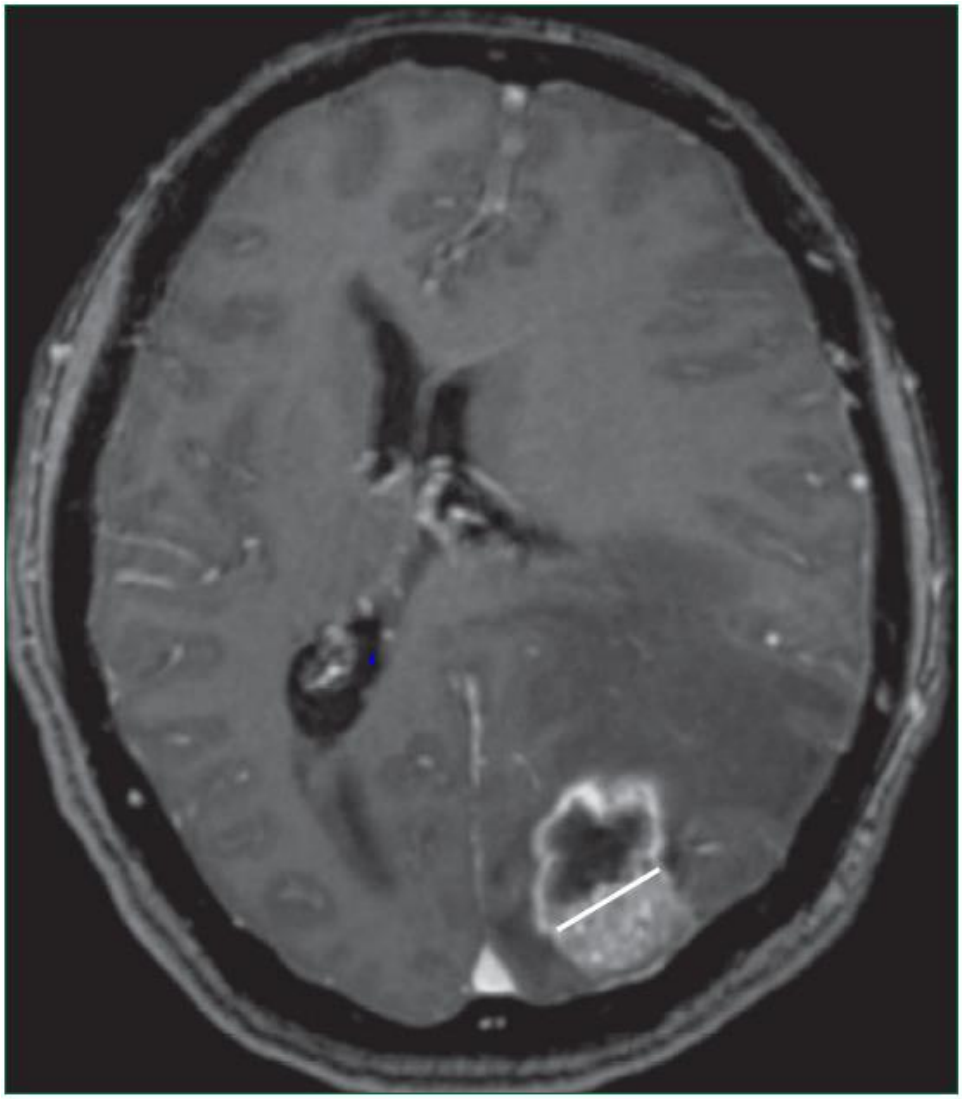


Figure 1: **Axial contrast-enhanced T1-weighted MRI of a brain metastasis from breast carcinoma with a partial solid and cystic component.**
Only the solid component is used for measurement of the longest diameter.

Gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure CNS lesions selected for response assessment.10,11 Suggested brain MRI specifications are detailed in the appendix. MRI is strongly encouraged as the default standard imaging technique, although CT with and without contrast could be considered in specific circumstances (e. g, countries with limited medical resources or contraindication for MRI).

Panel 1: **Response assessment of target and non-target lesions**

Target lesions	
Complete response	Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient

	is stable or improved clinically.
Partial response	At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease	At least a 20% increase in the sum longest diameter of CNS 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%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.
Non-target lesions: Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.	
Complete response	Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-complete response or non-progressive disease	Persistence of one or more non-target CNS lesion or lesions.
Progressive disease	Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

Tumour-response assessment

Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumour response is the primary endpoint. For studies in which objective response is not the primary endpoint, the protocol must specify prospectively whether entry is restricted to those with measurable disease or if patients with non-measurable disease are also eligible. Assignment of CNS response is independent of systemic disease response. CNS lesions are to be assessed according to RANO-BM criteria, whereas non-CNS lesions would most typically be assessed according to RECIST 1.1 criteria. Generally, CNS lesions should initially be re-assessed by MRI at protocol-specified intervals 6–12 weeks apart, although there might be specific circumstances in which longer (or shorter) intervals are desirable. For patients who remain stable for extended periods of time, a longer interval between scans might be appropriate. All baseline assessments should be done as close as possible to the treatment start and no more than 4 weeks before the beginning of treatment. For previously treated lesions, we recommend documentation of how each lesion was previously treated (e.g., stereotactic radiosurgery, whole brain radiotherapy, surgical resection). When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. All measurements should be recorded in metric notation. Target lesions should be selected on the basis of their size (longest diameter) and as those that can be measured reproducibly. For patients with recurrent disease who have multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be prioritised as target lesions for the response assessment. Lesions with prior local treatment (i.e., stereotactic radiosurgery or surgical resection) can be considered measurable if progression has occurred since the time of local treatment. However, careful consideration should be given to lesions previously treated with stereotactic radiosurgery, in view of the possibility of treatment effect, which we discuss below. Whether such lesions can be considered measurable should be specified prospectively in the clinical

protocol. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters. All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up.

Definition of best overall CNS response

Best overall CNS response is a composite of radiographical CNS target and non-target lesion responses (panel 1), corticosteroid use, and clinical status. For non-randomised trials in which CNS response is the primary endpoint, confirmation of partial response or complete response at least 4 weeks later is necessary to deem either one the best overall response.

Table 1: Summary of the response criteria for CNS metastases proposed by RANO-BM

	Complete	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest	≥20% increase in sum longest distance relative to nadir*
Non-target	None	Stable or improved	Stable or improved	Unequivocal progressive
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or	Stable or improved	Stable or improved	Worse*
Requirement for	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

At each protocol-specified timepoint, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 2 shows the additional corticosteroid and clinical status requirements to deem a partial response or complete response.

Assessment of target and non-target CNS lesions

While on study, all CNS target lesions should have their actual measurement recorded, even if very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) to be assigned an exact measure, a default value of 5 mm should be recorded on the case report form.

Lesions might coalesce during treatment. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum longest diameter 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 maximum longest diameter for the coalesced lesion.

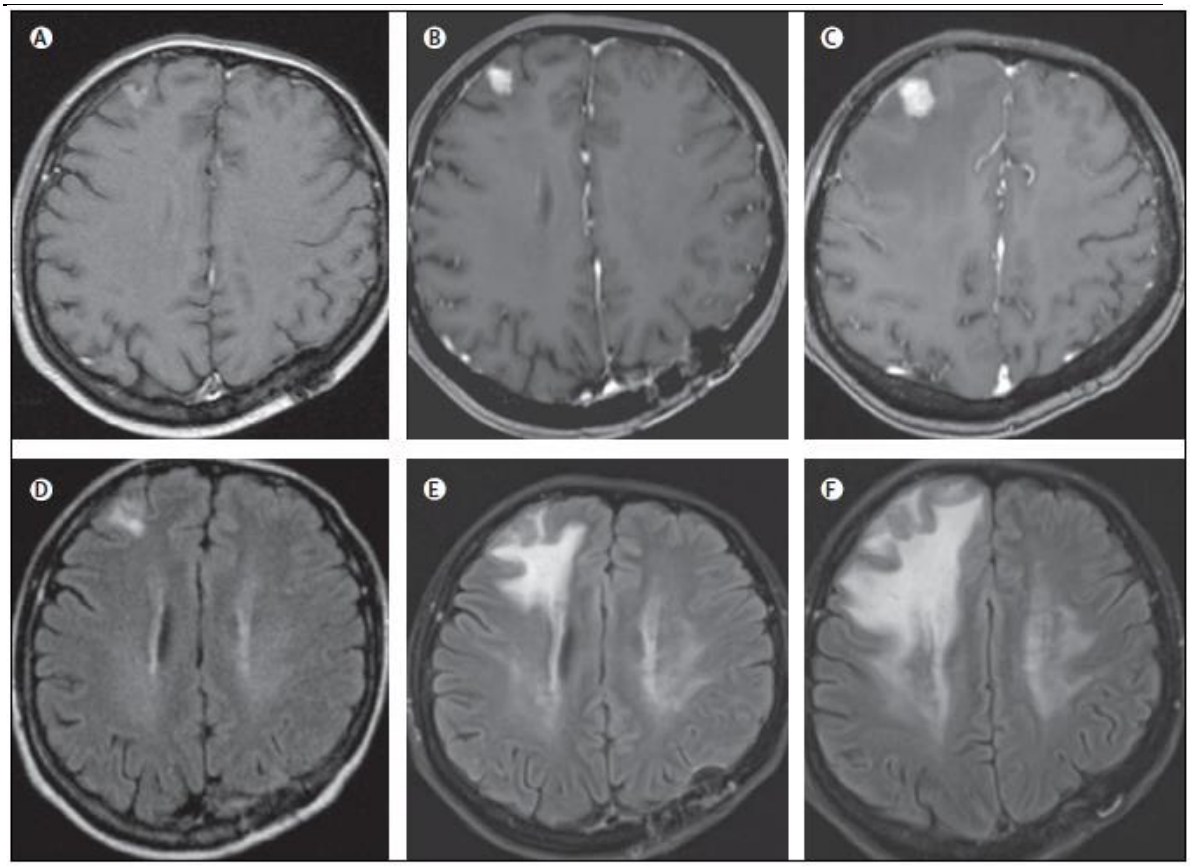


Figure 2: **True progression of brain metastasis**
Axial contrast-enhanced T1-w (A–C) and FLAIR images (D–F) of melanoma metastases before (A, D), during therapy with ipilimumab (B, E), and 3 months later (C, F).Note the constant increase in the extent of the contrast enhancing lesion and perifocal oedema.

New lesions can appear during treatment. The finding of a new CNS lesion should be unequivocal and not due to technical or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with slice thickness of 1.5 mm or less, the new lesion should also be visible in axial, coronal, and sagittal reconstructions of 1.5 mm or thinner projections. If a new lesion is equivocal, for example because of its small size (i.e., ≤5 mm), continued therapy can be considered, and a follow-up assessment will clarify if it really is new disease. If repeated scans confirm a new lesion, progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, however, new lesions alone cannot constitute progressive disease. Unequivocal progression of non-target lesions can merit discontinuation of therapy. When a patient also has measurable disease, to be deemed as having unequivocal progression on the basis of non-target disease alone there must also be an overall substantial worsening in non-target disease such that, even in the presence of stable disease or partial response in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

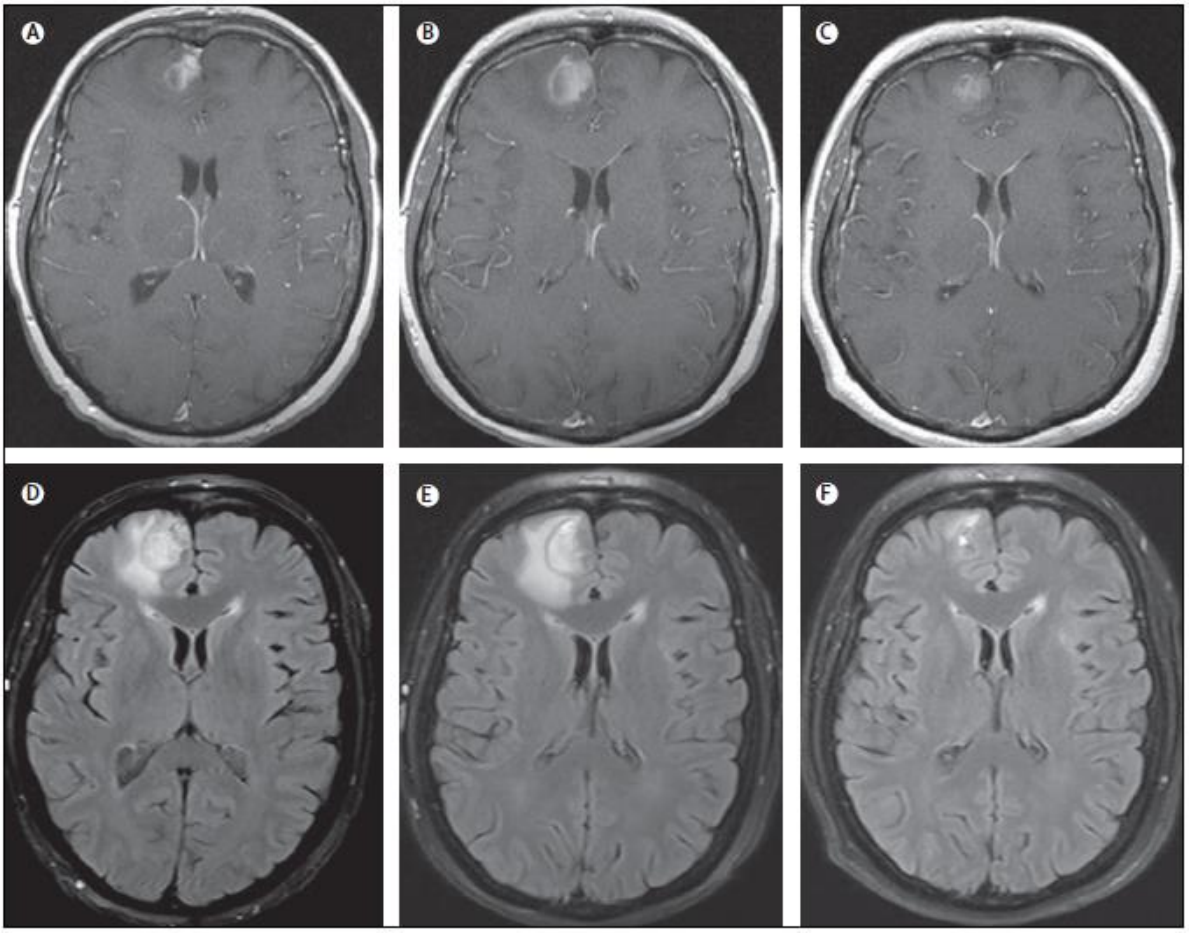


Figure 3: **Pseudoprogression of brain metastasis**
Axial contrast-enhanced T1-w (A–C) and FLAIR images (D–F) of melanoma metastases before (A, D), on ipilimumab (B, E), and 6 weeks after end of immunotherapy (C, F). Note the right frontal metastases with contrast enhancement and perifocal oedema (A, C), which increase under therapy (B, E) and resolve without change of therapy (C, F).

The RANO-BM group acknowledges the case of patients who have been treated with stereotactic radiosurgery12 or immunotherapy-based approaches, for whom there has been radiographical evidence of enlargement of target and non-target lesions, which do not necessarily represent tumour progression. If radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is needed to distinguish between true progression and treatment effect, in which case standard MRI alone is insufficient. The methods used to distinguish between true progression and treatment effect should be specified prospectively in the clinical protocol. Patients can be continued on protocol therapy pending further investigation with one or more of the following options.
The scan can be repeated at the next protocol-scheduled assessment or sooner, and generally within about 6 weeks. An investigator can choose a shorter time interval if progressive symptoms or other clinical concerns arise. Continued tumour growth might be consistent with radiographical progression, in which case the patient should leave the study (figure 2). Stabilisation and shrinkage of a lesion can be consistent with treatment effect, in which case the patient can stay in the study (figure 3). For patients with equivocal results even on the next restaging scan, the scan can be repeated again at a subsequent protocol-scheduled assessment or sooner, although surgery or use of an advanced imaging modality (in the case of stereotactic radiosurgery), or both, are strongly

encouraged. Surgical pathology can be obtained via biopsy or resection.

For lesions treated by stereotactic radiosurgery, additional evidence of tumour progression or treatment effect (radio necrosis) can be acquired with an advanced imaging modality, such as perfusion MRI, magnetic resonance spectroscopy, or 18FLT or 18FDG PET.13 On the basis of a literature review and extensive discussions, we found the literature insufficiently robust to conclude across all patients to distinguish between radiation

necrosis and true progression. Instead, we recommend clinical judgment and involvement of a multidisciplinary team. We recognise this recommendation is less than satisfactory and agree that more sensitive and specific methods to distinguish between treatment effect and tumour progression are needed. Note that these advanced imaging modalities have not been extensively studied with regards to immunotherapy-based approaches and therefore cannot be recommended to distinguish between tumour progression and immunerelated changes at present. Irrespective of the additional testing obtained, if subsequent testing shows that progression has occurred, the date of progression should be recorded as the date of the scan this issue was first raised. Patients can also have an equivocal finding on a scan (e.g., a small lesion that is not clearly new). Continued treatment is permissible until the next protocol-scheduled assessment. If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected. In patients receiving immunotherapy-based treatment, an initial increase in the number and size of metastases can be followed by radiographical stabilisation or regression.14 This pattern might be related to the mechanism of action of immunotherapy, including immune infiltrates, and the time to mount an effective immune response. Thus, progressive disease should not be solely defined by the appearance of new lesions but rather as a minimum 20% increase in the sum longest diameter of CNS target and new lesions, as unequivocal progression of existing enhancing non-target CNS lesions, as unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions, or as clinical decline related to the tumour. If immune response-related radiographical changes are suspected, we advise to not change treatment until a short interval scan is obtained. If the subsequent assessment confirms that progression has indeed date of the initial scan where progression was suspected.

Corticosteroid use and clinical deterioration

In the absence of clinical deterioration related to the tumour, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Patients with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumour do not qualify as having stable disease or progression. These patients should be observed closely, and if their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease, but if further clinical deterioration related to the tumour becomes apparent, they will be considered as having progression. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that patients who have a decrease in score on the Karnofsky performances scale from 100 or 90 to 70 points or less, a decrease of minimum 20 points from 80 or less, or a decrease from any baseline to 50 points or less, for at least 7 days, be considered as having neurological deterioration, unless this functional impairment is attributable to comorbid events, treatment related toxicity, or changes in corticosteroid dose.

APPENDIX 4: IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents) and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal 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 repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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, liver function tests (LFTs), CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium Difficile* toxin, and *cryptosporidia* (drug-resistant organism). In case of abdominal discomfort, consider imaging, e.g., X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (e.g., daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (e.g., statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP /LCI, iron studies. Consider imaging, e.g., 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 a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint x-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), cardiac MRI if possible, 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 isoenzyme; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; DLCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; HIV, human immunodeficiency virus; INR, international normalized ratio; LCI, liver 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

- The immune related AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, with patients is required
- irAEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice.
- 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.
- Steroid dosages in the table below are for oral or IV (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (e.g., mycophenolate mofetil [MMF]).
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy.
- Please also refer to latest ASCO practice guidelines on the management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy (Brahmer et al 2010)

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient 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	Thyrotoxic patients should be referred to an endocrinologist. If hypothyroid, replace with thyroxine 0.5 ~ 1.5 µg/kg/day (for the elderly or those with comorbidities, 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 (Patient 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 intravenous 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 endocrinologist's advice. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤ Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2 ~ 3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Unable to breathe at rest	Initiate 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 month. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms		Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1 ~ 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	2 Rash covers 10% ~ 30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral corticosteroids.	Continue study treatment.
	3 Rash covers > 30% BSA or grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5 ~ 1 mg/kg/day for 3 days then taper over 2 ~ 4 weeks For severe symptoms: IV methylprednisolone 0.5~ 1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Retreat when AE is resolved or improved to mild rash (Grade 1 ~ 2).
	4 Skin sloughing > 30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1 ~ 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
Hepatitis	**1** ALT or AST > ULN to 3 × ULN	Check liver function tests within 1 week and before the next dose to verify that there has been no worsening. If liver function tests are worsening, recheck every 48 ~ 72 hours until improvement is seen.	Continue study treatment if liver function tests are unchanged or improving. Hold study drug if liver function tests are worsening until improvement is seen.
	2 ALT or AST > 3 × to 5 × ULN	Recheck liver function tests within 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 liver function tests worsen, depending on clinical judgment.	Hold study treatment, treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	3 ALT or AST > 5 × to 20 × 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 intravenous (methyl) prednisolone 2 mg/kg/day. When liver function tests improve to grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade.
	4 ALT or AST > 20 × ULN	Initiate IV methylprednisolone 1 to 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening liver function tests despite steroids: • If on oral prednisolone, change to pulsed intravenous 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 1.5 × baseline or > ULN to 1.5 × ULN	Weekly repeat creatinine test. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5 to 3 × baseline or > 1.5 ~ 3 × ULN	Ensure hydration and review creatinine in 48 to 72 hours; if not improving, consider creatinine clearance measurement by 24-	Hold study treatment. If not attributed to drug toxicity, restart

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
		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.	treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3 × baseline or > 3 ~ 6 × ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1 to 2 mg/kg/day. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6 × 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 ~	Obtain a repeat blood glucose level at least every week. Management as per	Continue study treatment or hold treatment

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	13.9 mmol/L	local guideline.	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.	Hospitalize patient，refer patient to a diabetologist on management of hyperglycemia. 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	Hospitalize patient，diabetes management in local emergency department. Refer patient to a diabetologist for advice on insulin maintenance and monitoring.	
Ocular toxicity	**1** Asymptomatic eye examination/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	Seek urgent	Hold study

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	Posterior uveitis/panuveitis or significant symptoms	ophthalmology consultation. Initiate oral prednisolone 1 ~ 2 mg/kg and taper over at least 4 weeks.	treatment; retreatment may be considered when resolved/improved to Grade 0 ~ 1.
	4 Blindness (at least 20/200 or worse) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for emergency care. 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; retreatment may be considered.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency care and considering local consultation.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management as 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

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
			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; retreatment may be considered when resolved/improved to Grade 0 ~ 1.
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 improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0 to 1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. If not contraindicated, IV corticosteroids are given to manage infection.	Discontinue study treatment.
	1	Prescribe analgesics.	Continue

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
Myositis/Rhabdomyolysis	Mild weakness with/without pain	If CK is significantly elevated and patient has symptoms, consider oral corticosteroids and treat as Grade 2.	study treatment.
	2 Moderate weakness with/without pain	If CK is 3 × 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 to 1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and1 ~ 2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral corticosteroids over at least 4 weeks.	Hold study treatment until improved to Grade 0 to 1. Discontinue upon any evidence of myocardial involvement.
Myocarditis	**< 2** Asymptomatic but significantly elevated CK-MB/troponin or clinically significant intraventricular conduction delay	Initiate close monitoring of serum myocardial markers to assess cardiac status; consider referring patient tom 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. Tislelizumab may not be restarted in asymptomatic
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous methylprednisolone at	
	3		

Autoimmune Toxicity	Grade	Treatment Guidelines (Patient to Clinical Judgment)	Study Drug Management
	Severe symptoms with mild exertion	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 methylprednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	or less symptomatic patients unless cardiac findings recover to baseline.
	4 Is life-threatening		

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

Reference:

Brahmer JR, Drake CG, Wollner I, et al. Phase I Study of Single-Agent Anti–Programmed Death-1 (MDX-1106) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates. J Clin Oncol, 2010, 3167-317

APPENDIX 5: DOSE MODIFICATION GUIDELINES FOR CHEMOTHERAPY

For the purposes of this protocol, a chemotherapy cycle is defined as the administration of at least one chemotherapy component (i.e., carboplatin or pemetrexed). Cycles in which no chemotherapy component is given do not count toward the total number of chemotherapy cycles.

If only tislelizumab but no chemotherapeutic partner has been administered during a cycle, the cycle does not count toward the total number of chemotherapy cycles. For example, if 4 cycles of chemotherapy were planned, but no component of chemotherapy could be administered during Cycle 4, Cycle 5 counts as the 4^{th} cycle of this component.

Dose modification should be made in accordance with prescribing information and as per institutional guidelines.

- If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures/treatment and secondary prophylaxis instead of dose reductions for the next cycle.
- These provided triggers for dose modifications are recommendations only.
- Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration.
- All dose modifications should be made based on the worst toxicity grade.
- Carboplatin is only permitted to reduce to -25% doses once (from AUC 5 to AUC 4).

Criteria for Discontinuation of Chemotherapy Regimens

Except where specified above, both chemotherapy drugs 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 one the following criteria requires discontinuation:
  - AST or ALT > 5 × ULN for > 2 weeks
  - AST or ALT > 10 × ULN or
  - Total bilirubin > 5 × ULN or
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × ULN

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

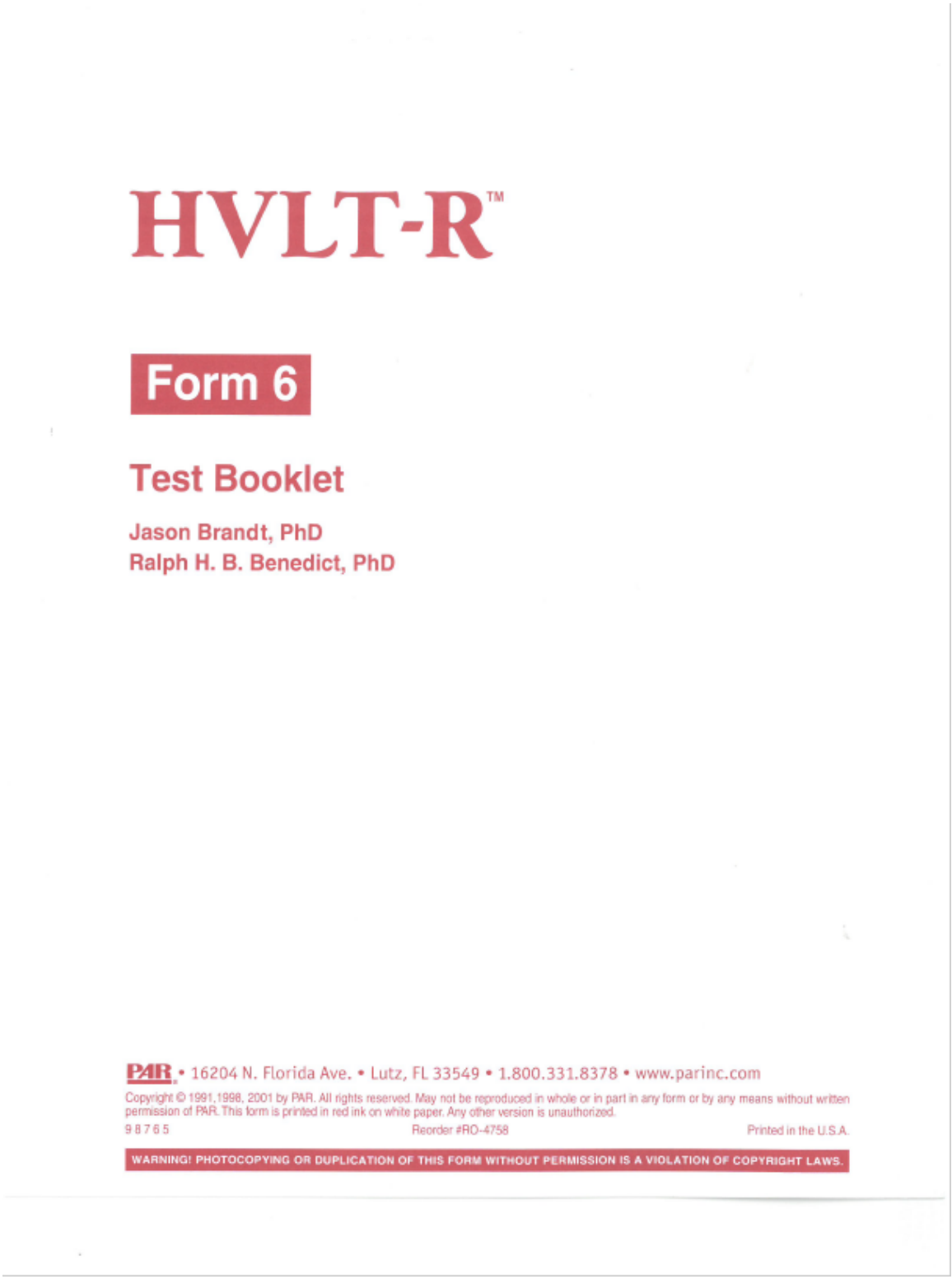
For toxicities not listed above, the investigator's medical judgment would determine whether the chemotherapy regimen should be discontinued, while considering the patient's well-being and local standards.

APPENDIX 6: PREEXISTING 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.

Acute disseminated encephalomyelitis	Addison 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 disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki’s disease
Lambert-Eaton myasthenic syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Kovanagi-Harada disease

APPENDIX 7: HOPKINS VERBAL LEARNING TEST-REVISED (HVLT-R) SCALE



HVLT-R™

Form 6

Test Booklet

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Learning Trial Instructions

Trial 1

Say the following:

I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?

- Repeat or paraphrase the instructions if necessary.
- Read the words at the rate of approximately one word every 2 seconds.
- If the individual does not spontaneously begin reporting words after the last word is read, say the following:

OK. Now tell me as many of those words as you can remember.

Record the responses verbatim (including repetitions and intrusions) in the Trial 1 column. When the individual indicates no more words can be recalled, proceed to Trial 2.

Trial 2

Say the following:

Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including all the words you told me the first time.

Use the same procedure as in Trial 1 to record the responses in the column for Trial 2. Then proceed to Trial 3.

Trial 3

Say the following:

I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.

Record the responses in the column for Trial 3 using the same procedure as in the previous trials.

NOTE: *Do not tell the respondent that recall of the words will be tested later.*

Delayed Recall Trial Instructions

After the 20-25 minute delay, say the following:

Do you remember that list of words you tried to learn before?

If the response is "No," remind the individual that you read the list three times and that he or she was asked to recall the words each time. Say the following:

Tell me as many of those words as you can remember.

Form 6

Semantic Categories: Fish, Parts of a Building, Weather Phenomena

Name _____ Sex _____ Age _____ years _____ months

Examiner _____ Date ____/____/____

Word List
SHARK
WALL
HERRING
RAIN
FLOOR
HAIL
CATFISH
ROOF
SALMON
STORM
CEILING
SNOW

Learning Trials			Delayed Recall (20-25 min.)
Trial 1	Trial 2	Trial 3	Trial 4
Total correct responses =			

Completion Time Start Time

Trial 3 _____ Trial 4 _____

Delayed Recognition Instructions

The Delayed Recognition (Forced Choice) trial is administered immediately after the Delayed Recall trial. Say the following:

> **Now I am going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list, or "No" if it was not.**

Read the words of the Delayed Recognition trial list in numerical order. Allow the individual as much time as needed to respond. You may use the prompt, **"Was hail on the list? Yes or no?"** The individual must give you a response for every word. If the individual is not sure, ask for a guess.

Delayed Recognition (Forced Choice)			
1. HAIL Y N	7. window Y N	13. HERRING Y N	19. SHARK Y N
2. bass Y N	8. CEILING Y N	14. SALMON Y N	20. hurricane Y N
3. SNOW Y N	9. canyon Y N	15. tornado Y N	21. elbow Y N
4. bank Y N	10. RAIN Y N	16. trout Y N	22. CATFISH Y N
5. FLOOR Y N	11. ladder Y N	17. melon Y N	23. WALL Y N
6. mustard Y N	12. STORM Y N	18. ROOF Y N	24. door Y N

Total number of true-positive responses ("hits"): _____ **/12** (no shading)

Semantically-related false-positive errors: _____ /6 (light shading)

Semantically-unrelated false-positive errors: _____ /6 (darker shading)

Total number of false-positive errors: _____ **/12**

	Raw score	*T* score
Total Recall (sum of total correct responses for Trials 1, 2, & 3)		
Delayed Recall (Trial 4)		
Retention (%) [(Trial 4 ÷ Higher score of Trials 2 and 3) x 100]		
Recognition Discrimination Index (Total no. of true-positives) – (Total no. of false-positives)		

Normative table (Appendix A): _____

4

APPENDIX 8: 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).
- An intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized male partner
- 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 (e.g., calendar, ovulation, symptothermal, or 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 has to be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential" AND "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 (i.e., through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Post-menopausal, defined as
    - ≥ 55 years of age with no spontaneous menses for ≥ 12 months
    - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

Extracted 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

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