CLINICAL STUDY PROTOCOL

Protocol Title:	Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients with Advanced Solid Tumors
Protocol Identifier:	BGB-900-101
Phase:	1-2
Investigational Products:	BGB-A333 and tislelizumab (BGB-A317)
EudraCT Number	2018-000265-37
Indication:	Advanced Solid Tumors
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1900 Powell Street, 5th Fl., Suite 500 Emeryville, CA 94608 USA
Sponsor Medical Monitor:	[redacted]
Original Protocol:	2 August 2017
Amendment 1.0	12 June 2018

FINAL PROTOCOL APPROVAL SHEET

Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients with Advanced Solid Tumors

BeiGene, Ltd. Approval:

INVESTIGATOR SIGNATURE PAGE

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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene or its designee

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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PROTOCOL AMENDMENT, VERSION 1: RATIONALE AND SUMMARY OF CHANGES

The main objectives for this amendment are to update the recommendation for management and reporting of irAE, and to align procedures to comply with company standards.

Throughout the protocol amendment, editorial changes and formatting revisions were made with the purpose of improving clarity and consistency. Additionally, the synopsis was updated to match changes made in the protocol body.

Substantial Changes:

- Throughout the protocol, BGB-A317 was replaced by its generic name tislelizumab
- Section 1.3.3 (Clinical Pharmacology), Section 1.3.4 (Prior Clinical Experience of Tislelizumab), Section 1.4.2 (Rationale for Combination of BGB-A333 and Tislelizumab in the Treatment of Advanced Solid Tumors), Section 1.4.4 (Rationale for Selection of Tislelizumab Dose), Section 5.3 (Overdose of Tislelizumab and Incorrect Administration of BGB-A333), and Section 5.4 (Dose Delay and Modification) were revised based on recent clinical analyses and to align with the latest version of the Tislelizumab IB (Edition 5.0, release date of 26 February 2018)
- Section 2 (Study Objectives and Endpoints) was revised and OS [redacted] was removed. This is an open-label study with relatively small sample size per cohort, it is unlikely to obtain clinically meaningful data on OS in the current study. As a result of removing OS, survival follow up period was removed
- Section 3.1 (Summary of Study Design) was revised and the following changes were made:
    - For Phase 2A and Phase 2B, approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. Eligibility criteria for these cohorts will be defined in future protocol amendments based on emerging clinical data. Sample size for Phase 2A and Phase 2B was adjusted throughout the protocol
- Section 3.1.1 (Phase 1A) was revised to fix a typographical error
    - The original protocol stated that "The MTD dose level is defined as the highest dose at which **≤ 33%** of the patients experience a DLT." It should be "The MTD dose level is defined as the highest dose at which **< 33%** of the patients experience a DLT."
- Section 3.3.3 (Safety Follow-up Period) was modified based on recent regulatory feedback on other studies of tislelizumab. Specifically,
    - Telephone contacts will be made at Day 60 and Day 90 to assess irAE and concomitant medications, regardless of whether or not the patient starts a new anticancer therapy
- Section 3.3.4 (Survival Follow-up Period) was removed
- Section 4.1 (Inclusion Criteria) was revised and the following changes were made:

- #7: Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤ 3 ULN for all patients. The purpose of this change is to align with CTCAE Grade
- #7: Removed coagulation inclusion criteria to align with standard sponsor language
- #7: A new criterion "HCC patients must meet Child-Pugh A classification" was added per request from one ethics committee in Australia
- General changes made to align with standard sponsor language for the study drugs

- Section 4.2 (Exclusion Criteria) was revised and the following changes were made:
  - #5 "With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management" was added
  - #9: eligibility for HCC patients with a history of HBV or HCV infection were modified (also impacts Schedule of Assessments Appendix 1)
  - #12: two additional CV risk factors (uncontrolled hypertension and recent episode of syncope/seizure) were added
  - #19: changed to "Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulation pathways)"
  - General changes made to align with standard sponsor language for the study drugs
- In Section 6.1.1 (Permitted Concomitant Medications and Therapy), requirement of antiviral therapy in patients with active hepatitis B was added based on recent regulatory feedback on other studies of tislelizumab
- In Section 6.2 (Prohibited or Restricted Concomitant Medications and Therapy), restrictions of hepatotoxic drugs, alcohol and addictive drugs in patients with HCC were added
- In Section 7.3.2.1 (Ophthalmologic Examination), eye exams were added based on recent regulatory feedback on other studies of tislelizumab
- In Section 7.3.7 (Hepatitis B and C testing), patients who have detectable HBV DNA at Screening will perform the viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc), at EOT visit, and when clinically indicated. This was added based on recent regulatory feedback on other studies of tislelizumab
- In Section 7.4 (Tumor and response evaluation), the following revisions were made:
  - Tumor response will be assessed by the investigators using RECIST v1.1 (see Appendix 9). Additional information on new lesions will be collected according to iRECIST (see Appendix 10) and sponsor will derive tumor response using iRECIST as an exploratory assessment
  - Imaging of the brain (MRI or CT) at baseline (≤ 28 days of the first dose of study drug(s)) is required for all patients
- In Section 8.6.2 (Reporting SAE), documentation method for SAE reporting is modified.
- Appendix 1 (Schedule of Assessments) was updated to align with changes in assessment

- In Appendix 1 and Appendix 2, CK and CK-MB tests were added to align with BeiGene's safety monitoring guideline for the risk of myocarditis/myositis
- In Appendix 2, clarification of required clinical laboratory assessments
- Appendix 8 (irAE Evaluation and Management) was updated to include ASCO guideline and recent regulatory feedback on other studies of tislelizumab
- Appendix 11 (Child-Pugh classification scoring system) was added due to the addition of inclusion criterion on HCC patients

SYNOPSIS

Name of Sponsor:	BeiGene, Ltd.
Investigational Products:	BGB-A333 and tislelizumab (BGB-A317)
Title of Study:	Phase 1-2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-PD-L1 Monoclonal Antibody BGB-A333 Alone and in Combination with Anti-PD-1 Monoclonal Antibody Tislelizumab in Patients with Advanced Solid Tumors
Protocol Identifier:	BGB-900-101
Phase of Development:	1-2
Study Centers:	Up to 20 centers in Australia, New Zealand, Taiwan, Europe, and the United States
Duration of Patient Participation:	This study will consist of 3 periods: 1. **Screening Period** is within 28 days prior to first study drug administration. 2. **Treatment Period** starts with the first study drug administration and ends when the patient discontinues study treatment 3. **Safety Follow-up Period** Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow up Visit (to occur within 30 days [± 7 days] after the last dose of study drug (s) or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (±14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy. AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the Investigator as stable, the patient is lost to follow-up, or the patient withdraws consent.

Study Objectives:

Phase 1A (Dose Escalation for BGB-A333 Monotherapy) and

Phase 1B (Dose Confirmation for BGB-A333 and Tislelizumab Combination)

Primary:

- To assess the safety and tolerability of BGB-A333 alone and in combination with tislelizumab (BGB-A317) in patients with advanced solid tumors
- To determine the maximum tolerated dose (MTD), if any, and RP2D for BGB-A333 alone and in combination with tislelizumab

Secondary:

- To assess the preliminary antitumor activity of BGB-A333 alone and in combination with tislelizumab
- To characterize the pharmacokinetics (PK) of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 alone and in combination with tislelizumab

Exploratory:

- [redacted]

Phase 2A (BGB-A333 Monotherapy Dose Expansion) and

Phase 2B (BGB-A333 and Tislelizumab Combination Dose Expansion)

Primary:

- To assess objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of BGB-A333 alone and in combination with tislelizumab in patients with selected tumor types

Secondary:

- To assess other tumor assessment outcomes ie, duration of response (DOR) progression-free survival (PFS), and disease control rate (DCR) per RECIST version 1.1
- To characterize safety and tolerability of BGB-A333 alone and in combination with tislelizumab
- To characterize the PK of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 and tislelizumab

Exploratory:

- [redacted]

Study Endpoints:

Phase 1A (Dose Escalation for BGB-A333 Monotherapy) and

Phase 1B (Dose Confirmation for BGB-A333 and Tislelizumab Combination)

Primary Endpoints:

- Safety and tolerability: The safety of BGB-A333 alone and in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, relevant physical examination, electrocardiograms and laboratory assessments as needed
- The MTD, if any, and Recommended Phase 2 Dose (RP2D) for BGB-A333 alone and in combination with tislelizumab will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data

Secondary Endpoints:

- Efficacy evaluations: ORR, DOR, and DCR will be determined by investigators based on RECIST version 1.1
- PK: Individual BGB-A333 and tislelizumab concentrations and PK parameters will be tabulated by dose cohort
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients by dose cohort who develop detectable antidrug antibodies

Exploratory Endpoints:

Phase 2A (BGB-A333 Monotherapy Dose Expansion) and

Phase 2B (BGB-A333 and Tislelizumab Combination Dose Expansion)

Primary Endpoint:

- Efficacy evaluations: ORR will be determined by investigators based on RECIST version 1.1

Secondary Endpoints:

- DOR, PFS, and DCR will be determined by investigators based on RECIST version 1.1
- Safety and tolerability: The safety of BGB-A333 alone and in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE

Version 4.03, relevant physical examination, electrocardiograms and laboratory assessments as needed

- PK: Individual concentrations and PK parameters of BGB-A333 and tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable antidrug antibodies (ADAs)

Exploratory Endpoints:

[redacted]

Study Population

Phase 1: Patients with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors who have progressed during or after the standard therapy or for which treatment is not available, not tolerated or refused.

Phase 2: Arm 1: Patients with locally advanced and metastatic urothelial carcinoma who have progressed during or after treatment with platinum-based chemotherapy or who could not tolerate platinum-based chemotherapy.

In addition, Sponsor may consider other tumor types including but not limited to non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), gastric cancer (GC), and microsatellite instability (MSI)-high cancer, etc. The eligibility criteria for patients with these tumor types will be defined in future protocol amendments.

Key Eligibility Criteria

Adult patients (≥ 18 years of age or acceptable age according to local regulations, whichever is older at the time of voluntarily signing of informed consent) with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors. All patients are also required to have an ECOG PS score of ≤ 1, and adequate organ function.

Test Product, Dose, and Mode of Administration:

Phase 1A: BGB-A333 Dose Escalation

- BGB-A333: approximately 3 to 5 dose levels or dosing regimens may be tested. The initial plan is to test 450 mg, 900 mg and 1350 mg every 3 weeks (Q3W), intravenously (IV). A lower dose (eg, 225 mg Q3W), intermediate doses or higher doses (eg, 1800 mg and/or 2250 mg Q3W) may be tested based on preliminary safety, tolerability, PK, and antitumor activities of BGB-A333 observed in dose levels tested. Different dosing regimens every 2 weeks (Q2W) or every 4 weeks (Q4W) may also be explored

Phase 1B: BGB-A333 and Tislelizumab Combination Dose Confirmation

- BGB-A333: The SMC will make a recommendation on the selection of BGB-A333 dose based on available safety, efficacy, PK and exploratory data from Phase 1A. If this initial dose in combination is deemed not tolerated, lower dose(s) or alternative dosing regimens of BGB-A333 may be tested in combination with tislelizumab
- Tislelizumab: 200 mg (Q3W, IV). Alternative dosing regiments may be explored

Phase 2A: BGB-A333 Dose Expansion

- BGB-A333: at RP2D determined in Phase 1A

Phase 2B: BGB-A333 and Tislelizumab Combination Dose Expansion

- BGB-A333 and Tislelizumab: at the dosing regimen determined in Phase 1B

Study Design

This is an open-label, multicenter, nonrandomized Phase 1 and Phase 2 clinical trial. This study consists of the following phases:

- Phase 1A (BGB-A333 dose escalation): approximately 3-5 dose levels or dosing regimens will be tested in patients with advanced solid tumors. Additional dose levels could be tested if needed. The modified 3+3 design will be used in the dose escalation. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached.
- Phase 1B (BGB-A333 and tislelizumab dose confirmation): a cohort of approximately 6 patients with solid tumors will be treated with BGB-A333 and tislelizumab (200 mg, Q3W, IV). The SMC will make a recommendation on the selection of BGB-A333 dose based on available safety, efficacy, PK and exploratory data from Phase 1A. If the initial dose combination is deemed not tolerated, additional cohorts of patients may be enrolled to evaluate lower doses or alternative dosing regimens of BGB-A333 and tislelizumab.
- Phase 2A (BGB-A333 dose expansion): approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider enrolling 20-40 patients with other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data.
- Phase 2B (BGB-A333 and tislelizumab dose expansion): approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider enrolling 20-40 patients with other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data.

All patients will receive study drug until 1) they are no longer considered to be achieving clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent.

In Phase 1A (BGB-A333 monotherapy), if patients progress on BGB-A333 without other safety concerns, these patients may be treated with a higher dose of BGB-A333 that is deemed to be well tolerated by SMC. The decision to modify the dose of BGB-A333 must be discussed with the sponsor's medical monitor and documented in the study records.

In Phase 1A and Phase 2A (BGB-A333 monotherapy), if patients progress on BGB-A333 monotherapy without other safety concerns, these patients may receive combination of BGB-A333 and tislelizumab at doses that are deemed to be well tolerated by SMC. The decision to add tislelizumab to patients treated with BGB-A333 alone must be discussed with the sponsor's medical monitor and documented in the study records.

Study Assessments

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study.

DLT Assessment

For Phase 1A (BGB-A333 dose escalation), at least 3 patients evaluable for dose-limiting toxicity (DLT) assessment will be enrolled per dose level. Dose escalation will proceed to the next dose level if no DLT is observed in the first 3 DLT-evaluable patients. Otherwise, if a DLT has occurred, the cohort is expanded to at least 6 patients. If there is no additional DLT in the first 6 DLT-evaluable patients, dose escalation will continue to the next level. Dose escalation will stop when there are 2 or more DLTs in 6 patients within the same dose level. If 2 or more DLTs are reported in 6 patients at a dose level, a minimum of 6 patients will be enrolled on the next lower dose level, or an intermediate dose level may be evaluated if recommended by the SMC. The MTD dose level is defined as the highest dose at which < 33% of the patients experience a DLT. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached.

DLTs will be assessed among evaluable patients within 21 days after the first dose of BGB-A333. For dose escalation decision, only DLTs occurring within the first 21 days will be evaluated. For determination of MTD and RP2D, clinically significant toxicities (eg, irAE) will also be considered.

A SMC will be established and includes both the sponsor and at least 2 investigators. The SMC will review all available safety, efficacy, PK and exploratory data and make recommendation on dose escalation, dose modification and dose selection for Phase 1B and Phase 2.

Definition of DLT

All toxicities or adverse events will be graded according to the NCI-CTCAE Version 4.03. The occurrence of any of the following toxicities within 21 days after the first dose of BGB-A333 if judged by the Investigator as related to BGB-A333 will be considered a DLT.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days
2. Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of 38.3°C or a sustained temperature of 38°C for >1 hour)
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia

6. Grade 4 anemia (life-threatening)

Non-hematologic:

1. Grade 4 or above toxicity
2. Grade 3 toxicity lasting more than 7 days despite optimal supportive care

Note: The following AEs will not be considered as DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 rash
- Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, LDH)

In addition, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by SMC.

Patients who received < two-thirds (67%) of the assigned dose of BGB-A333 (eg, because the infusion had to be stopped due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level.

Tumor Assessments

Radiological assessment of tumor-response status should be performed approximately every 9 weeks (for Q3W dosing) in the first year, then every 12 weeks thereafter. If other dosing intervals are explored (Q2W or Q4W), radiological assessment of tumor response will be performed approximately every 8 weeks.

Tumor response will be assessed by Investigators based on the RECIST version 1.1. Additional information on new lesions will be collected according to iRECIST Guidelines and sponsor will derive tumor response using iRECIST as an exploratory assessment.

For immune therapies, such as BGB-A333 and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with study drug(s) until PD is confirmed by repeated imaging at least 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. The following criteria must be met in order to continue study drug treatment in patients with suspected pseudoprogression:

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

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

Statistical Methods

Descriptive statistics will be used to summarize the demographic, disease characteristic, efficacy and safety data. No statistical hypotheses are planned in this study.

Analysis Populations

- Safety Population includes all patients who received at least 1 dose of study drug(s). It will be the population for the safety and efficacy analyses
- Efficacy Evaluable Population includes all dosed patients who have evaluable disease at baseline, and at least one evaluable post-baseline tumor response assessment unless any clinical PD or death occurred before the first post-baseline tumor assessment
- DLT Evaluable Population includes patients who received at least two-thirds (67%) of the assigned dose of BGB-A333 during the DLT observation period and had sufficient safety evaluation or patients who experienced DLT within DLT observation period
- The PK analysis population includes all patients with valid PK sampling after treatment with study drug(s)

Safety Analysis:

Safety will be determined by the spontaneous reporting of adverse events and by laboratory values (hematology, serum chemistry, coagulation, and urinalysis). Vital signs, physical examination and ECG findings will also be used in determining the safety profile. The severity of adverse events will be graded according to the CTCAE v4.03. The incidence of DLT events, treatment-emergent AEs (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Efficacy Analysis:

The efficacy endpoints based on RECIST v1.1 (ie, ORR, DOR, PFS, and DCR) will be summarized to evaluate the antitumor activities of BGB-A333 alone or in combination with tislelizumab.

- ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by investigator using RECIST v1.1. ORR and its 95% confidence interval (CI) will be summarized in the Safety Population and Efficacy Evaluable Population
- DOR is defined as the time from the first determination of an objective response per RECIST

v1.1, until the first documentation of progression or death, whichever occurs first

- DCR is defined as the proportion of patients with best overall response of CR, PR and SD. It will be summarized similarly as ORR
- PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of disease progression assessed by investigator using RECIST v1.1 or death, whichever occurs first
- Waterfall plots of maximum tumor shrinkage per patient will be presented
- [redacted]

Statistical methods will be described in detail in the Statistical Analysis Plan.

Sample Size Considerations:

The study plans to enroll approximately 58 to 168 patients.

- Phase 1A (BGB-A333 dose escalation): Approximately 12 to 30 patients with advanced solid tumors in 3-5 dose levels or dosing regimens per modified 3+3 design
- Phase 1B (BGB-A333 and tislelizumab combination): Approximately 6 patients with advanced solid tumors in one combination dosing regimen. An additional 12 patients may be enrolled to test different dosing regimens
- Phase 2A (BGB-A333 dose expansion): Approximately 20 patients with UC. Additional 20-40 patients with other tumor types (to be defined in future protocol amendments based upon emerging data) may be enrolled
- Phase 2B (BGB-A333 and tislelizumab combination dose expansion): Approximately 20 patients with UC. An additional 20-40 patients with other tumor types (to be defined in future protocol amendments based upon emerging data) may be enrolled

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration curve
BOR	best overall response
CBC	complete blood count
CDC	complement-dependent cytotoxicity
CI	confidence interval
C_{max}	maximum observed plasma concentration
COPD	chronic obstructive pulmonary disease
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
C_{trough}	trough serum concentration
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EOT	end of treatment
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
GC	gastric cancer
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HED	human equivalent dose
HIV	human immunodeficiency virus

Abbreviation	Definition
HNSCC	head and neck squamous cell carcinoma
ICF	informed consent form
ICH	International Council on Harmonisation
ICU	intensive care unit
IEC	Independent Ethics Committee
IND	Investigational New Drug
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
km	the serum BGB-A333 concentration at which BGB-A333 is eliminated at 50% of V_{max}
mAB	monoclonal antibody
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
NaF-PET	sodium fluoride proton emission tomography
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
ORR	objective response rate
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamics; progressive disease
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
Q2W	every 2 weeks
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RSI	reference safety information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SMC	Safety Monitoring Committee

Abbreviation	Definition
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
TK	toxicokinetics
TSH	thyroid stimulating hormone
UC	urothelial carcinoma; urothelial cancer
ULN	upper limit of normal
V_d	volume of distribution
V_{max}	the maximum elimination rate
WHO	World Health Organization

1. INTRODUCTION AND RATIONALES

1.1. Introduction

BGB-A333 is a humanized IgG1-variant monoclonal antibody (mAB) against programmed cell death 1-ligand 1 (PD-L1), the ligand of an immune check point- receptor, programmed cell death-1 (PD-1). It is being developed for the treatment of human malignancies.

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

Several anti-PD-1 and anti-PD-L1 agents have been approved for the treatment of a number of histologically distinct tumors. Tumor types selected in the Phase 2 portion of this study may include but are not limited to urothelial cancer (UC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), gastric cancer (GC), and microsatellite instability (MSI)-high cancer as they are representative of tumors for which there is evidence for clinical responses to other immunotherapies and those for which there is supportive correlative pathologic data suggesting that the PD-1/PD-L1/2 pathway is important for tumor progression.

1.2. BGB-A333 as a PD-L1 Blocker

PD-L1 is expressed on various hematopoietic cells, including T cells, dendritic cells, monocytes, and in many nonhematopoietic tissues, including lung, vascular endothelium, liver, skin, etc. It is believed that PD-L1 plays an important role in immune modulation of tumor progression by inducing key inhibitory signaling in the T-cells and other immune cells when engages to its receptors PD-1 and B7-1 (also known as CD80). The PD-L1/PD-1 and PD-L1/B7-1 signaling cascades negatively regulate T-cell receptor activation and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-L1 expression is significantly increased in tumor cells and tumor- associated immune cells in the presence of stimulating cytokines such as IFN-γ and IFN-α in the tumor microenvironment. Furthermore, the increased PD-1 expression in tumor-infiltrating lymphocytes and/or increased PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human tumors including but not limited to melanoma, UC, NSCLC, RCC, SCCHN, GC, and Merkel cell carcinoma (MCC). Several anti-PD-L1 antibodies have been recently approved for the treatment of several cancers. Thus, PD-L1 is an established target for cancer immunotherapy.

1.2.1. Pharmacology

BGB-A333 binds to the extracellular domain of human PD-L1 with high specificity and affinity (K_D = 0.072 nM) as demonstrated by target binding assays and SPR characterization. It competitively blocks PD-L1 binding to both PD-1 and B7-1, inhibiting PD-1 mediated negative signaling in T-cells. In in vitro cell-based assays, BGB-A333 consistently and dose-dependently enhances the functional activities of human T-cells and pre-activated, primary peripheral blood mononuclear cells (PBMCs). In addition, BGB-A333 has demonstrated antitumor activity in several cancer xenograft models, including the A431 human epidermoid carcinoma model and the SK-MES-1 human squamous cell carcinoma model, where the PBMCs or human NK92 cells are co-transplanted with the human cancer cells A431 or

SK-MES-1, respectively. Similarly, the anti-murine PD-L1 surrogate antibody, Ab161, has shown antitumor activity in the syngeneic CT26 colon cancer model.

BGB-A333 has been engineered in the heavy chain constant region to eliminate the Fc effector functions. BGB-A333 has no or very low bindings to C1q or all FcγRs, including FcγRI, FcγRIIA, FcγRIIB, and FcγRIIIA, in in vitro binding assays, suggesting a low or no antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC), etc. effector functions in humans. BGB-A333 does not induce ADCC or CDC in the cell-based assays.

1.2.2. Toxicology

BGB-A333 binds to the cynomolgus monkey and human PD-L1 with similar affinity, but does not bind to mouse PD-L1 due to the significant sequence divergence from human and mouse PD-L1. Therefore, the cynomolgus monkey is to be considered the relevant species for nonclinical safety evaluation.

The toxicity and safety profile of BGB-A333 was characterized in single dose toxicology studies in mice and monkeys and in a 13-week repeat dose toxicology study in monkeys. The tissue cross reactivity was evaluated in the normal frozen tissues from both humans and monkeys. These pivotal studies were conducted following Good Laboratory Practice (GLP) regulations. The cytokine release assays were also evaluated using fresh human whole blood cells. The single dosing regimens were spanning from the intended human doses to more than 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanning to 5-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and cross-species PD-L1 binding activities.

No apparent toxicity was noted in both mice and monkeys following a single dose up to 250 mg/kg in mice and in monkeys following a repeat dose up to 100 mg/kg biweekly for 13 weeks. The toxicokinetics (TK) profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional without gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no apparent changes in clinical pathology or histopathology were noted in these studies. Immunogenicity with positive antidrug antibody (ADA) against BGB-A333 was noted in the single dose monkey study with 1 of 2 monkeys in 30 mg/kg and 100 mg/kg dose groups and in the repeat dose study with 12/12, 6/12, and 3/12 of animals at doses of 10, 30, and 100 mg/kg, respectively. The ADAs against BGB-A333 were demonstrated to have neutralization activities in a cell based assay and, except for the low dose of 10 mg/kg, appeared to have no apparent impact on the systemic exposure in the middle (30 mg/kg) or high dose (100 mg/kg) groups.

The tissue cross reactivity of BGB-A333 was evaluated in normal human and cynomolgus monkey frozen tissues using immunohistochemistry method, with appropriate positive and negative controls. Some staining was observed on the trophoblast cell membrane and cytoplasm of human placenta, which was consistent with published literature. Some staining was observed in the cytoplasm of smooth muscle in the human tissues as well as monkey tissues. No increase of the cytokine release from human whole blood cells after treatment with BGB-A333 was observed in in vitro evaluations.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No relevant tissue cross-reactivity was found in human and monkey tissues and, no effect on cytokine release was observed in human whole blood assay. The TK 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 BGB-A333 in 13-week monkey toxicity study was to be considered 100 mg/kg. The safety profile of BGB-A333 is considered adequate to support first-in-human dose safely and ethically.

Refer to the Investigator's Brochure (IB) for more detailed information of BGB-A333.

1.2.3. Comparison Between BGB-A333 and OtherAnti-PD-L1 Agents

Three anti-PD-L1 agents (atezolizumab, avelumab, and durvalumab) have received United States Food and Drug Administration (FDA) approval for use in various indications.

The binding affinity of BGB-A333 to PD- L1 is higher than atezolizumab and durvalumab and comparable with that of avelumab. Similar to atezolizumab and durvalumab, the heavy chain constant region in BGB-A333 was modified to eliminate Fc effector functions so that it does not have ADCC, ADCP, or CDC effects.

Table 1. Comparison Between BGB-A333 and Other Anti-PD-L1 Agents

	IgG	Binding Affinity, nM	ADCC
atezolizumab	IgG1 variant	1.75	No
avelumab	IgG1 WT	0.0467	Yes
durvalumab	IgG1 variant	0.667	No
BGB-A333	IgG1 variant	0.072	No

Abbreviations: IgG = immunoglobulin; IgG1 = immunoglobulin G1; WT = wild type.
Sources: Package inserts for:
atezolizumab: https://www.accessdata fda.gov/drugsatfda_docs/label/2016/761041lbl.pdf
avelumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf
durvalumab: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761069s000lbl.pdf
BGB-A333 IB

1.3. Tislelizumab as a PD-1 Blocker

Immune check point-inhibitory receptor, PD-1 is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes. It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade negatively regulates T-cell receptor and attenuate T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of PD-1 ligand, PD-L1, is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as IFN-γ and IFN-α in the tumor microenvironment. Furthermore, the increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor and tumor-associated

stromal cells is observed in many types of solid human tumors including, but not limited to [redacted] Several anti-PD-1 agents have been approved for the treatment of several cancers. Thus, PD-1 is an established target for cancer immunotherapy.

1.3.1. Pharmacology

Tislelizumab is a humanized, IgG4-variant mAB against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (K_D=0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed death-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 PBMCs. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which PBMCs were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to FcγRIIIA and Complement 1q, a subunit of complement 1, by in vitro assays, suggesting either low or no ADCC or CDC effects in humans (Labrijn 2009).

Please refer to the tislelizumab IB for additional details regarding nonclinical studies of tislelizumab.

1.3.2. Toxicology

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

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assay. The TK 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 NOAEL of tislelizumab in the 13-week monkey toxicity study was to be considered 30 mg/kg. The safety profile of tislelizumab is considered adequate to support first-in-human (FIH) dose safely and ethically.

Please refer to the tislelizumab IB for more detailed information on the toxicology of tislelizumab.

1.3.3. Clinical Pharmacology

In Phase 1 BGB-A317_Study_001 and Study BGB-A317-102, interim pharmacokinetic (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 every 2 weeks (Q2W) and 2.0 mg/kg, 5.0 mg/kg, 200 mg every 3 weeks (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). Maximum observed plasma concentration (C_{max}) and area under the plasma concentration curve (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 one dose of 200 mg Q3W (Phase 1a, Part 3 and Study BGB-A317-102) showed tislelizumab concentrations between the range of concentrations observed after 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 show a systemic CL of tislelizumab of 0.173 L/day, volume of distribution (V_d)in the central and peripheral compartments of 2.89 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.

1.3.4. Prior Clinical Experience of Tislelizumab

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

Please refer to the tislelizumab IB for more detailed information on efficacy and safety of tislelizumab.

1.3.4.1. BGB-A317_Study_001 (Data cut off 28August 2017)

Study BGB-A317_Study_001 is a two-stage study consisting of a Phase 1a dose-escalation and dose-finding component with 3 parts to establish the maximum tolerated dose (MTD), if any, a recommended Phase 2 dose (RP2D[s]) for the Phase 1b, and a flat dose (fixed dose) followed by a Phase 1b component to investigate efficacy in select tumor types in indication expansion arms and to further evaluate safety and tolerability of tislelizumab.

As of 28 August 2017, in Phase 1a, 116 patients had received tislelizumab at dose regimens including 0.5 mg/kg, 2 mg/kg, 5 mg/kg, or 10 mg/kg Q2W; 2 mg/kg or 5 mg/kg Q3W; and 200 mg Q3W. In Phase 1b, 323 patients had received tislelizumab in Phase 1b across 9 indication-expansion cohorts.

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

Preliminary Safety

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

Preliminary efficacy

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

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

1.3.4.2. Study BGB-A317-102 (Data cut off 28 August 2017)

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

Overall, for the 123 patients in Study BGB-A317-102, the median age was 54.0 years, 66.7% of the population was male, and 100.0% of patients were Asian (Chinese). The median number of prior anti-cancer therapy regimens was 2 (range: 0 to 9). The median treatment exposure duration was 1.78 months (range: 0 to 8.0) and the median study follow-up duration was also 1.78 months (range: 0.0 to 8.0). As of 28 August 2017, there were 113 patients (91.9%) on study in Study BGB-A317-102.

Preliminary Safety

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

Preliminary efficacy data are not yet available.

1.3.4.3. Immune-related Reactions

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

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

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

1.4. Study Rationales

1.4.1. Rationale for BGB-A333 as a Monotherapy

BGB-A333 is an anti-PD-L1 antibody. A large body of literature supports the role of PD-L1 in immune modulation of tumor progression. Several anti-PD-L1 antibodies have been recently approved for the treatment of several cancers. BGB-A333 is expected to provide similar clinical benefit as the approved anti-PD-L1 antibodies.

1.4.2. Rationale for Combination of BGB-A333 and Tislelizumab in the Treatment of Advanced Solid Tumors

Anti-PD-1 and anti-PD-L1 monotherapies have shown clinical benefit in a variety of cancers, although the response rates are still somewhat low in most tumor types. The goal of combination therapy is to improve clinical response rate and increase duration of response. The emerging scientific evidence supporting the potential benefit of this combination is summarized below.

The mechanisms of action of anti-PD-1 and anti-PD-L1 are different albeit with overlapping elements. Anti-PD-1 (such as tislelizumab) blocks PD-1 binding to PD-L1 and PD-L2, thus inhibiting PD-1-mediated negative signaling in T-cells. Besides binding to PD-1, PD-L1 also interacts with B7-1 (also known as CD80) and this interaction can also exert inhibitory effects on immunity (Butte 2007). In

addition, a recent study by Hui et al. has demonstrated that CD28 is a primary target for PD-1-mediated immune inhibition (Hui 2017). PD-L1 inhibitors block the interaction between PD-L1 and CD80 (B7-1), which in turn releases inhibitory signals to T-cells, enhances T-cell expansion and prevents T-cell energy induction (Park 2010). Therefore, combination of anti-PD-1 and anti-PD-L1 antibodies can potentially elicit stronger antitumor immunity through blockade of multiple complementary immune-suppressive signals in tumor microenvironments.

Several preclinical studies have demonstrated potential synergy between anti-PD-1 and anti-PD-L1 antibodies. In the mouse MCA205 sarcoma model, combination of anti-PD-1 and anti-PD-L1 antibodies showed stronger tumor growth inhibition effect than administration of anti-PD-1 antibody alone (Hamid 2016) (Figure 1). In a recent study, mouse tumor models of anti-PD-1 sensitivity (MC38 tumor) and anti-PD-1 resistance (AT3 tumor) were compared (Ngiow 2015) (Figure 2). Administration of an anti-PD-1 antibody significantly increased PD-L1 expression on intratumor T-cells and myeloid cells in both anti-PD-1 sensitive and resistant tumors. However, the expression level of PD-L1 in anti-PD-1 resistant tumors remained lower than anti-PD-1 sensitive tumors at all times (Ngiow 2015). In the anti-PD-1 resistant tumor model (AT3), anti-PD-L1 antibody alone or in combination with anti-PD-1 antibodies suppressed the tumor growth. Thus, the anti-PD-L1 antibody might be an effective therapy to treat PD-1 resistant tumors.

Figure 1. Combination of PD-1 and PD-L1 in Mouse MCA205 Sarcoma Model (Hamid 2016)

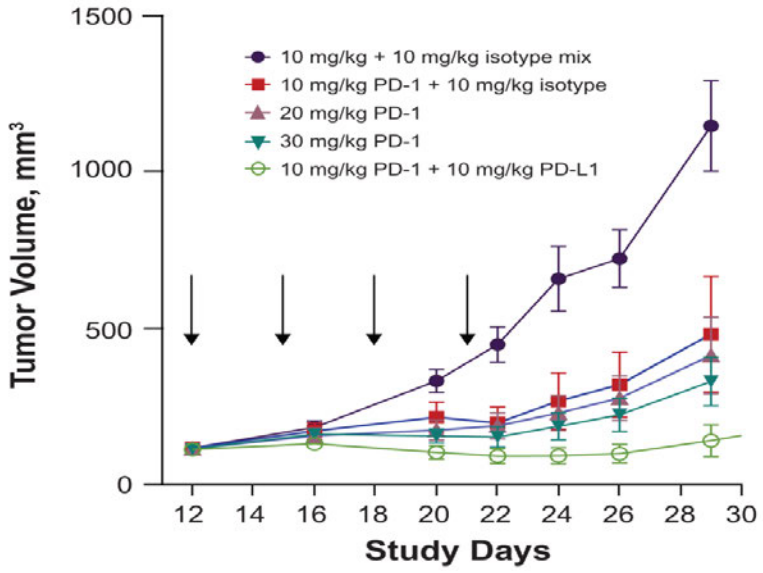
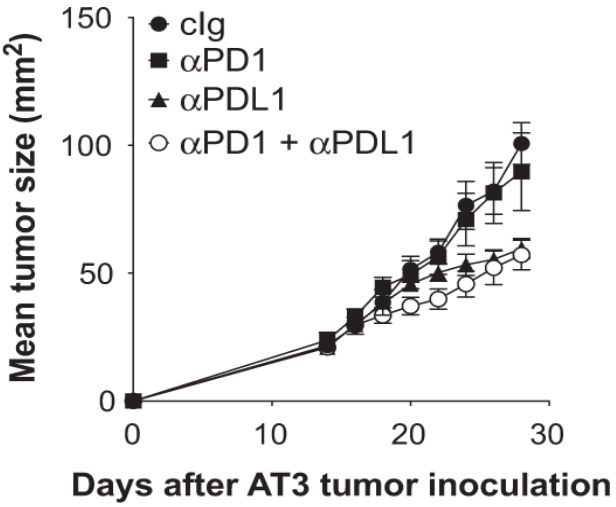


Figure 2. Combination of PD-1 and PD-L1 inPD-1 resistant model (AT3 Tumor) (Ngiow 2015)



Results from an ongoing Phase 1 study of combination of MEDI0680 (an anti-PD–1 antibody) with durvalumab (an anti-PD-L1 antibody) showed an acceptable safety profile with evidence of antitumor activity in patients with advanced malignancies (Hamid 2016). In particular, in higher dose cohorts (10 to 20 mg/kg) of MEDI0680, objective response rate (ORR) was 50% (n=14). One CR was observed in urothelial carcinoma and 6 PRs were observed in mixed tumor types including RCC (3 PR), NSCLC (2 PR) and HNSCC (1 PR). These provide preliminary clinical evidence that the combination of PD-1 and PD-L1 blockers are well tolerated with notable antitumor activity.

1.4.3. Rationale for Selection of BGB-A333 Starting Dose

1.4.3.1. Compartmental Pharmacokinetic Model

BGB-A333 has demonstrated a favorable toxicology and safety pharmacology profile in nonclinical studies. Early clinical development of BGB-A333 will be conducted in patients who have advanced cancer and progressed after standard-care treatment.

The relevant species for preclinical safety evaluation is cynomolgus monkey, because BGB-A333 binds to and is pharmacologically active towards PD-L1 in cynomolgus monkey, but does not bind to mouse. The Kd for BGB-A333 binding to cynomolgus monkey PD-L1 is similar to that for human, whereas the binding to mouse PD-L1 is not detectable.

Two studies (P16-050-YD, P16-050-CD) were conducted in cynomolgus monkeys to assess the PK and TK of BGB-A333. Three pharmacology studies were conducted in xenograft (A431, SK-MES-1) or syngeneic (CTG26WT) mouse tumor models to assess the pharmacodynamics (PD) of BGB-A333 and a surrogate PD-L1 antibody (Ab161) respectively. A PK/PD model was developed to describe the kinetics of BGB-A333 using PK data from cynomolgus monkeys and PD data (tumor growth inhibition) from the mouse studies.

A 2 -compartmental model describes the PK of BGB-A333. In this model, the dose was administered into the central compartment, from which elimination was modeled as occurring in parallel, by a first-order linear clearance pathway, presumably mediated by the reticuloendothelial system, and a nonlinear pathway, presumably by target-mediated clearance.

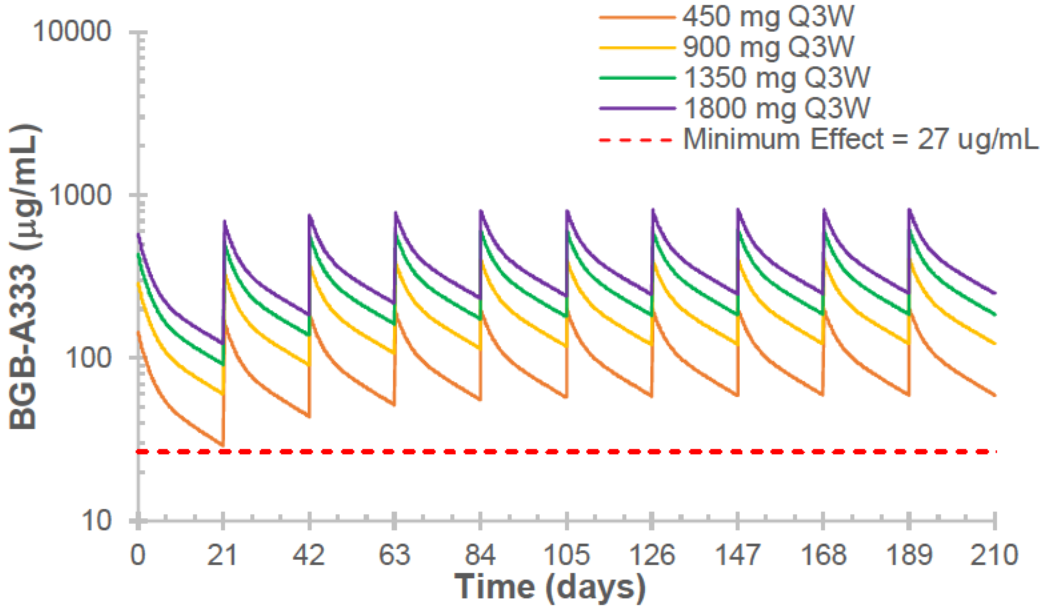
PK parameters were derived from the serum concentration-time profiles of BGB-A333 from different dose regimens in TK studies which were conducted in cynomolgus monkeys (P16-050-YD, P16-050-CD). V_{max} (the maximum elimination rate) and km (the serum BGB-A333 concentration at which BGB-A333 is eliminated at 50% of V_{max}) characterized the nonlinear target-mediated clearance. The estimated nonlinear clearance is characterized by V_{max} (0.317 mg/kg/day) and km (and 5.45 µg/mL), respectively. The linear clearance was estimated to be 6.39 mL/kg/day, which is consistent with the clearance of cynomolgus monkey reported in the literature (Deng 2011). The results demonstrated that the 2-compartment model with linear and nonlinear clearance in parallel adequately described the PK profiles of BGB-A333 in cynomolgus monkey.

1.4.3.2. Pharmacologically Active Dose of BGB-A333

The minimum efficacious dose was determined by the mouse tumor models (A431, SK-MES-1, and CT26WT). Various weekly doses of BGB-A333 were associated with tumor growth inhibition in xenograft mouse models. The dose of 3 mg/kg weekly was determined to be the minimum effective dose with significant tumor growth inhibition, which was converted to human equivalent dose (HED) as approximately 3 mg/kg (FDA guidance), and with model-predicted efficacious trough levels of approximately 27 µg/mL.

The PK parameters derived from monkeys were allometrically scaled to obtain the human PK parameters. Based on km, the nonlinear target-mediated clearance pathway is largely saturated at clinically relevant doses, and the nonspecific linear clearance pathway mediated by reticuloendothelial system becomes the major determinant for BGB-A333 clearance. The linear clearance of BGB-A333, 0.212 L/day (for 70 kg subject) and steady state volume of distribution of 5.95 L were subsequently used to simulate the multiple-dose PK profiles in human subjects (Figure 3). The projected steady state $T_{½}$ of BGB-A333 in human is approximately 20 days.

Figure 3. Simulated PK Profiles of BGB-A333



Abbreviations: PK = pharmacokinetics; Q3W = every 3 weeks

1.4.3.3. Recommendation of the First-in-Human Dose of BGB-A333

A number of agents targeting both sides of the PD-1/PD-L1 interaction are currently in clinical development. Although this is the first clinical study with BGB-A333 in humans, there is extensive clinical experience with other anti-PD-L1 mABs. Clinical doses of several recently approved anti-PD-L1 antibodies are defined as 10 mg/Q2W (avelumab and durvalumab) or 1200 mg Q3W (atezolizumab). The chosen starting dose and range for this study is based on the monkey safety data and the projected human efficacious dose from preclinical mice data. The starting dose of 450 mg (approximately 6 mg/kg for 75 kg patients) to be evaluated in this FIH study is selected to provide a partial pharmacologically active dose. The dose-escalation of 450, 900, 1350, and 1800 mg BGB-A333 is designed to rapidly achieve dose levels at which clinical activity would be observed while maintaining an adequate safety margin. It is anticipated that the PK of dosing BGB-A333 in humans every 3 weeks at or beyond the starting dose ($\geq$ 450 mg) is in linear range, and it will maintain the serum BGB-A333 concentrations above the trough concentration (27 µg/mL) needed for the minimum effect, which was determined from observed data of tumor xenograft studies and simulated human PK profiles.

Predicted safety margins were determined in support of the proposed doses selected for this FIH clinical study. The NOAEL for BGB-A333 was determined to be 100 mg/kg intravenously (IV) Q2W in cynomolgus monkeys (P16-050-YD, P16-050-CD). Observed exposures to BGB-A333 in cynomolgus monkeys were compared with the predicted exposure in humans in terms of C_{max} and AUC to derive the predicted safety margins.

The predicted safety margins for the recommended FIH doses are listed in Table 2.

Table 2. Predicted Safety Margins

Proposed Human Doses	Predicted Steady State AUC_{τ} (µg·d/mL)	Predicted Steady State C_{max} (µg/mL)	Safety Margin	
			AUC	C_{max}
450 mg Q3W	2030	202	11.6	15.9
900 mg Q3W	4146	408	5.68	7.89
1350 mg Q3W	6262	613	3.76	5.25
1800 mg Q3W	8378	819	2.81	3.93

Abbreviations: Q3W = every 3 weeks; AUCτ: area under the serum concentration-time curve within the interval; AUC-based safety margin = $AUC_{14,cyno,Day71} \times \frac{3}{2} \div AUC_{21,human,SS}$ = 15708.8 µg·day/mL × $\frac{3}{2}$ ÷ $AUC_{21,human,SS}$; C_{max} = calculated or observed maximum serum concentration of steady state; $Cmax_{,cyno,Day71} \div Cmax_{,human,SS}$ = 3221.7 mg/mL ÷ $Cmax_{,human,SS}$

Following multiple doses of 450 mg IV BGB-A333 Q3W, this dosing regimen is predicted to produce:

- An AUC with a 11.6-fold safety margin relative to the observed exposure in cynomolgus monkeys and a C_{max} with a 15.9-fold safety margin relative to the observed C_{max} in cynomolgus monkeys, based on the NOAEL of 100 mg/kg IV BGB-A333 Q2W (total 7 doses) in Study P16-050-CD
- A 2.81-fold and 3.93-fold safety margin on AUC and C_{max}, respectively, relative to the highest dose, 1800 mg IV Q3W, based on a NOAEL of 100 mg/kg IV BGB-A333 Q2W (total 7 doses) in Studies P16-050-CD

A fixed dose regimen is chosen to reduce dosing errors and to ensure ease of preparation. Published data shows that PK variability is similar for fixed dose dosing regimens and body weight-based dose regimens (Zhang 2011; Wang 2009). The 3-weekly schedule is chosen based on the projected steady state $t_{½}$ of BGB-A333 in humans (20 days) and maintained steady state trough levels above minimum efficacious level. This selection of dose range will allow for optimal characterization of the BGB-A333 PK/PD and safety.

The Safety Follow-up Period is determined based on the predicted PK profile of proposed doses of BGB-A333. The Follow-up Period is anticipated to be at minimum 5 times the elimination half-life of compounds with a linear PK; the serum half-life of BGB-A333 is estimated to be 20 days. A 90-day follow-up time is chosen to allow for adequate safety coverage as the highest dose of BGB-A333 (1800 mg IV) will fall below the sub-therapeutic level.

1.4.4. Rationale for Selection of Tislelizumab Dose

The PK, safety, and efficacy data obtained from FIH study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of 200 mg IV Q3W was selected for further evaluation.

Rates of treatment-related AEs and serious adverse events (SAEs) observed in patients receiving 2 mg/kg and 5 mg/kg Q2W and Q3W were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg Q2W ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg Q3W.

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

Additionally, no unexpected treatment-related AEs occurred in the 200 mg fixed dose cohort (BGB-A317_Study_001, Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n = 13), 3 patients (23%) had a best overall response (BOR) of partial response (PR), 4 patients (31%) had a BOR of stable disease (SD), and 6 patients (46%) had a BOR of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg Q3W.

In conclusion, tislelizumab 200 mg Q3W is the recommended initial dose for combination with BGB-A333. Additional dosing regimens may be explored.

1.5. Benefit-Risk Assessment

Urothelial carcinoma is the ninth most common cancer overall worldwide. Platinum-based chemotherapy is the standard of care in previously untreated patients with metastatic urothelial carcinoma, and is associated with an overall survival of around 9–15 months (von der Maase 2005, De Santis 2012). The prognosis for patients who relapse after platinum-based chemotherapy is poor, with median survival ranging from 5 to 7 months (Bellmunt 2009). Anti-PD-L1 agents (atezolizumab, durvalumab and avelumab) showed good tolerability in this patient population and the objective response rate is higher in patients with PD-L1 expression (Hahn 2017, Powles 2017, and Apolo 2017).

More than 500 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg) and in combination. The safety profile is consistent with known class effects of anti-PD-1 antibodies, and included mostly mild/moderate AEs. Very few Grade 3 or 4 irAEs have been observed, which are generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion on safety profile of tislelizumab, please refer to the tislelizumab IB.

Given the unmet medical need in patients with advanced UC, the benefit/risk assessment based on available tislelizumab Phase 1 data and the publication from other PD-1 or PD-L1 inhibitors is considered favorable.

A Safety Monitoring Committee (SMC) will be established and will review regularly monitor the safety and activity of BGB-A333 alone and in combination with tislelizumab. SMC will review all available safety, efficacy, PK and exploratory data and make recommendation on dose selection and safety management throughout the study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives for Phase 1A (Dose Escalation for BGB-A333 Monotherapy) and Phase 1B (Dose Confirmation for BGB-A333 and Tislelizumab Combination)

2.1.1. Primary Objectives

- To assess the safety and tolerability of BGB-A333 alone and in combination with tislelizumab in patients with advanced solid tumors
- To determine the MTD, if any, and RP2D for BGB-A333 alone and in combination with tislelizumab

2.1.2. Secondary Objectives

- To assess the preliminary antitumor activity of BGB-A333 alone and in combination with tislelizumab
- To characterize the PK of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 alone and in combination with tislelizumab

2.1.3. Exploratory Objectives

- [redacted]

2.2. Study Objectives for Phase 2A (BGB-A333 Monotherapy Dose Expansion) and Phase 2B (BGB-A333 and Tislelizumab Combination Dose Expansion)

2.2.1. Primary Objectives

- To assess ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of BGB-A333 alone and in combination with tislelizumab in patients with selected tumor types

2.2.2. Secondary Objectives

- To assess other tumor assessment outcomes (ie, duration of response [DOR], progression-free survival [PFS], and disease control rate [DCR]) per RECIST v1.1
- To characterize safety and tolerability of BGB-A333 alone and in combination with tislelizumab
- To characterize the PK of BGB-A333 alone and in combination with tislelizumab
- To assess host immunogenicity to BGB-A333 and tislelizumab

2.2.3. Exploratory Objectives

- [redacted]

- [redacted]
- [redacted]

2.3. Study Endpoints for Phase 1

2.3.1. Primary Endpoints

- Safety and tolerability: The safety of BGB-A333 alone and in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per the National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE Version 4.03, relevant physical examination, electrocardiograms (ECGs) and laboratory assessments as needed
- The MTD, if any, and RP2D for BGB-A333 alone and in combination with tislelizumab will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data

2.3.2. Secondary Endpoints

- Efficacy evaluations: ORR, DOR, and DCR will be determined by investigators based on RECIST version 1.1
    - ORR is defined as the proportion of patients who had confirmed complete response (CR) or partial response (PR) assessed by investigator using RECIST version 1.1. ORR and its 95% confidence interval (CI) will be summarized in the Safety Population and Efficacy Evaluable Population
    - DOR is defined as the time from the first determination of an objective response per RECIST version 1.1, until the first documentation of progression or death, whichever occurs first
    - DCR is defined as the proportion of patients with best overall response of CR, PR and SD. It will be summarized similarly as ORR
- PK: Individual BGB-A333 and tislelizumab concentrations and PK parameters will be tabulated by dose cohort
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients by dose cohort who develop detectable antidrug antibodies

2.3.3. Exploratory Endpoints

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

[redacted]

2.4. Study Endpoints for Phase 2

2.4.1. Primary Endpoint

- Efficacy evaluations: ORR will be determined by investigators based on RECIST version 1.1. The ORR is defined as the proportion of patients who had confirmed CR or PR assessed by investigator using RECIST version 1.1. ORR and its 95% CI will be summarized in the Safety Population and Efficacy Evaluable Population

2.4.2. Secondary Endpoints

- DOR, PFS, and DCR will be determined by investigators based on RECIST version 1.1
  - PFS is defined as the time from the date of the first dose of study drug(s) to the date of the first documentation of disease progression assessed by investigator using RECIST v1.1 or death, whichever occurs first
- Safety and tolerability: The safety of BGB-A333 alone and in combination with tislelizumab will be assessed throughout the study by monitoring AEs and SAEs per NCI-CTCAE Version 4.03, relevant physical examination, ECGs, and laboratory assessments as needed
- PK: Individual concentrations and PK parameters of BGB-A333 and tislelizumab
- Immunogenicity: Immunogenic responses to BGB-A333 and tislelizumab will be assessed by summarizing the number and percentage of patients who develop detectable ADAs

2.4.3. Exploratory Endpoints

- [redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, nonrandomized Phase 1 and Phase 2 clinical trial. The study design schematic is presented in Figure 4. For all study procedures see Section 7 and Appendix 1.

This study consists of the following phases:

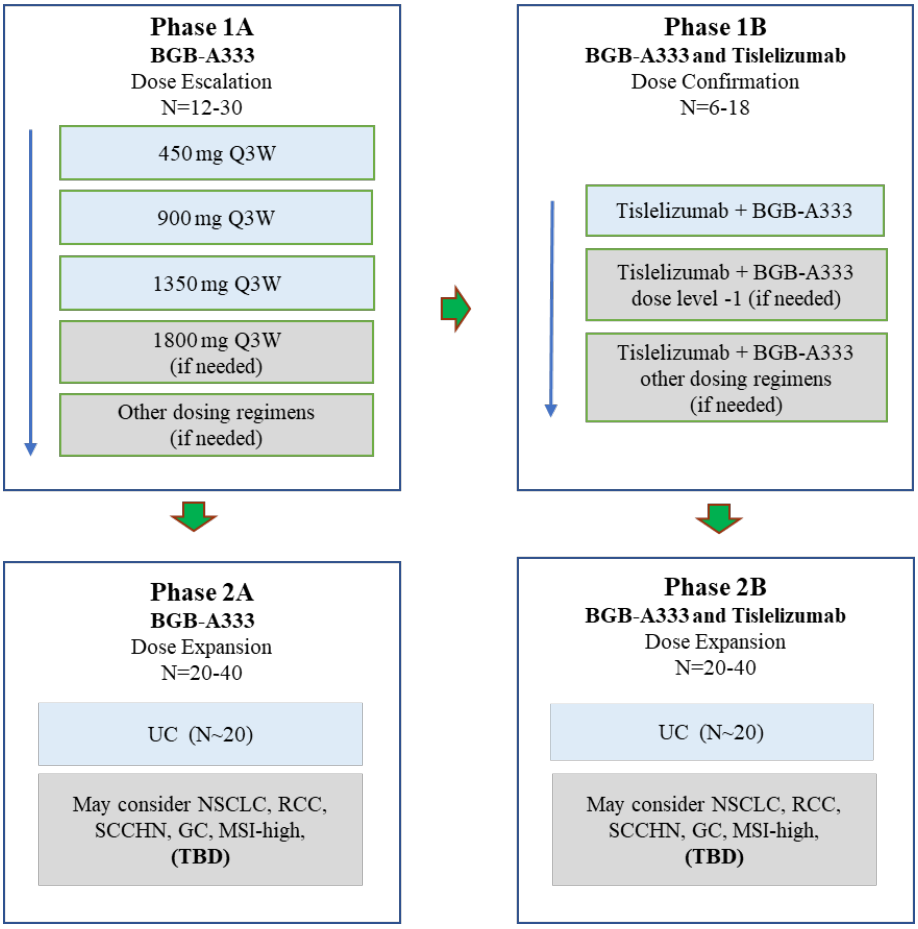
- Phase 1A (BGB-A333 dose escalation): approximately 3-5 dose levels will be tested in patients with advanced solid tumors. Additional dose levels or dosing regimens could be tested if needed. The modified 3+3 design will be used in the dose escalation. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached
- Phase 1B (BGB-A333 and tislelizumab dose confirmation): a cohort of approximately 6 patients with solid tumors will be treated with BGB-A333 and tislelizumab (200 mg, Q3W, IV). The SMC will make a recommendation on the selection of BGB-A333 dose based on available safety, efficacy, PK and exploratory data from Phase 1A. If the initial dose combination is deemed not tolerated, additional cohorts of patients may be enrolled to evaluate lower doses or alternative dosing regimens of BGB-A333 and tislelizumab
- Phase 2A (BGB-A333 dose expansion): approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data
- Phase 2B (BGB-A333 and tislelizumab dose expansion): approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data

All patients will receive study drug until 1) they are no longer considered to be achieving clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent.

In Phase 1A (BGB-A333 monotherapy), if patients progress on BGB-A333 without other safety concerns, these patients may be treated with a higher dose of BGB-A333 that is deemed to be well tolerated by SMC. The decision to modify the dose of BGB-A333 must be discussed with the sponsor's medical monitor and documented in the study records.

In Phase 1A and Phase 2A (BGB-A333 monotherapy), if patients progress on BGB-A333 monotherapy without other safety concerns, these patients may receive combination of BGB-A333 and tislelizumab at doses that are deemed to be well tolerated by SMC. The decision to add tislelizumab to patients treated with BGB-A333 alone must be discussed with the sponsor's medical monitor and documented in the study records.

Figure 4. Study Schema



Abbreviations: GC = gastric cancer; NSCLC = non-small cell lung carcinoma; UC = urothelial carcinoma; RCC = renal cell carcinoma; SCCHN = squamous cell carcinoma of the head and neck; MSI = microsatellite instability-high; Q3W = every 3 weeks; TBD = to be determined.

3.1.1. Phase 1A (BGB-A333 Dose Escalation)

For Phase 1A (BGB-A333 dose escalation), at least 3 patients evaluable for dose-limiting toxicity (DLT) assessment will be enrolled per dose level. Dose escalation will proceed to the next dose level if no DLT is observed in the first 3 DLT-evaluable patients. Otherwise, if a DLT has occurred, the cohort is expanded to at least 6 patients. If there is no additional DLT in the first 6 DLT-evaluable patients, dose escalation will continue to the next level. Dose escalation will stop when there are 2 or more DLTs in 6 patients within the same dose level. If 2 or more DLTs are reported in 6 patients at a dose level, a minimum of 6 patients will be enrolled on the next lower dose level, or an intermediate dose level may be evaluated if recommended by the SMC. The MTD dose level is defined as the highest dose at which < 33% of the patients experience a DLT. At least 6 evaluable patients should be enrolled at the MTD level, the RP2D level or at the highest dose level tested if MTD is not reached.

DLTs will be assessed among evaluable patients within 21 days after the first dose of BGB-A333. For dose escalation decision, only DLTs occurring within the first 21 days will be evaluated. For determination of MTD and RP2D, clinically significant toxicities (eg, irAE) will also be considered.

The SMC will review all available safety, efficacy, PK, and exploratory data and make a recommendation on dose escalation and dose selection for Phase 1B and Phase 2.

3.1.2. Phase 1B (BGB-A333 and Tislelizumab Combination Dose Confirmation)

After completion of Phase 1A, a cohort of approximately 6 patients with solid tumors will be treated with BGB-A333 and tislelizumab (200 mg, Q3W, IV). The SMC will make a recommendation on the selection of BGB-A333 dose based available safety, efficacy, PK, and exploratory data.

- If 2 or more DLTs are reported in these 6 patients, a minimum of 6 patients will be enrolled to a lower dose level (DL-1) if recommended by an SMC
- Similarly, if 2 or more DLTs are reported at DL-1, a minimum of 6 patients will be enrolled to a next lower dose level (DL-2) if recommended by an SMC

The SMC will review all available safety, efficacy, PK, and exploratory data and make a recommendation on dose selection for Phase 2B.

3.1.3. Phase 2A (BGB-A333 Dose Expansion)

Approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data.

Eligible patients will receive BGB-A333 and tislelizumab that are deemed to be well tolerated in Phase 1A.

3.1.4. Phase 2B (BGB-A333 and Tislelizumab Dose Expansion)

Approximately 20 patients with UC will be enrolled. In addition, Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with the additional tumor types will be defined in future protocol amendments based upon emerging data.

Eligible patients will receive BGB-A333 and tislelizumab that are deemed to be well tolerated in Phase 1B.

3.2. Enrollment Priority

The first priority is to enroll patients to Phase 1A. After completion of Phase 1A and the RP2D for BGB-A333 monotherapy has been determined, Phase 2A (patients with UC) and Phase 1B (advanced solid tumors) will be open for enrollment in parallel. Phase 2B will be open after completion of Phase 1B.

3.3. Study Periods

This study consists of the following 3 periods. See Section 7 and Appendix 1 for study procedures to be conducted in each period.

3.3.1. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of study drug(s). Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure (refer to Appendix 1 for details). Patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer will take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Archival tumor tissues (if available) must be collected for the purpose of biomarker analysis. If no archival samples are available, a fresh tumor biopsy at baseline is highly recommended. Refer to Section 7.6 for details.

3.3.2. Treatment Period

After completing all screening activities, patients confirmed to be eligible by the sponsor will be treated with BGB-A333 alone or in combination with tislelizumab.

All patients will receive study drug until 1) they are no longer considered to be achieving clinical benefit, 2) unacceptable toxicity, or 3) withdrawal of informed consent.

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

An optional biopsy will be taken at the end of treatment visit for patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism (written informed consent is required prior to obtaining fresh tumor biopsies).

3.3.3. Safety Follow-Up Period

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (to occur within 30 [±7 days] after last dose of the study drug(s) or before initiation of a new anticancer treatment, whichever occurs first). In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days and 90 days (±14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy. AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the Investigator as stable, the patient is lost to follow-up, or the patient withdraws consent.

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

The End of Treatment visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up visit, provided that it occurred 30 days (± 7 days) after the last study treatment. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.4.

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

3.4. Patient Discontinuation and Study Completion

3.4.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression, should be followed for assessments of antitumor activity and safety.

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

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

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

3.4.2. Patient Discontinuation from Study (End of Study for an Individual Patient)

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

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

3.4.3. Study Completion or Termination

The study completion is defined as the timepoint when the final data for the study were collected after the last patient has made the final visit to the study location.

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 adverse events in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

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

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

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

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

3.5. DLT Definition

All toxicities or AEs will be graded according to the NCI-CTCAE Version 4.03. The occurrence of any of the following toxicities within 21 days after the first dose of BGB-A333 if judged by the Investigator as related to BGB-A333 will be considered a DLT.

Hematologic:

1. Grade 4 neutropenia lasting >7 days
2. Grade 3 febrile neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of 38.3^oC or a sustained temperature of 38^oC for >1 hour)
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life-threatening)

Non-hematologic:

1. Grade 4 or above toxicity

2. Grade 3 toxicity lasting more than 7 days despite optimal supportive care

Note: The following AEs will not be considered as DLTs:

- Grade 3 endocrinopathy that is adequately controlled by hormonal replacement
- Grade 3 AE of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumors)
- Grade 3 rash
- Grade 3 to Grade 4 laboratory abnormalities that are not associated with clinical sequelae (eg, LDH)

In addition, clinically important or persistent toxicities that are not included above may also be considered a DLT following review by SMC.

Patients who received <two-thirds (67%) of the assigned dose of BGB-A333 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level.

4. STUDY POPULATION

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

4.1. Inclusion Criteria

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

1. Able to provide written informed consent and can understand and comply with the requirements of the study
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place)
3. For Phase 1 only: patients with histologically or cytologically confirmed advanced or metastatic, unresectable solid tumors who have progressed during or after standard therapy or for which treatment is not available, not tolerated or refused
4. For Phase 2 only:
    a. Arm 1: Patients with locally advanced and metastatic urothelial carcinoma who have progressed during or after treatment with platinum-based chemotherapy or who could not tolerate platinum-based chemotherapy.
    b. Sponsor may consider other tumor types including but not limited to NSCLC, RCC, SCCHN, GC, MSI-high cancer, etc. The eligibility criteria for patients with these tumor types will be defined in future protocol amendments
5. Patient must have at least one measurable lesion as defined per RECIST v1.1

    Note: The target lesion(s) selected have not been previously treated with local therapy or the target lesion(s) selected that are within the field of prior local therapy have subsequently progressed as defined by RECIST v1.1.
6. Has Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1
7. Has adequate organ function as indicated by the following laboratory values:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, platelets ≥ 75 × 10^9/L, hemoglobin ≥ 90 g/L. Note: Patients must not have required a blood transfusion or growth factor support ≤ 14 days before sample collection
    b. Serum creatinine ≤ 1.5 × upper limit of normal (ULN), or estimated GFR ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 7)
    c. Aspartate transaminase (AST) and alanine aminotransferase (ALT) ≤ 3 × ULN
    d. Serum total bilirubin ≤ 1.5 X ULN (total bilirubin must be < 3 X ULN for patients with Gilberts syndrome)
    e. For hepatocellular carcinoma (HCC) patients only, patient must meet the Child-Pugh A classification for liver function as assessed within 7 days before the first dose of study drug(s) (Appendix 11).
8. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 120 days after the last dose of study drug (s), and have a negative urine or serum pregnancy test ≤ 7 days of the first dose of study drug(s)

9. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for ≥ 120 days after the last dose of study drug(s)

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll

1. Active leptomeningeal disease or uncontrolled brain metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided they are asymptomatic and radiologically stable without the need for corticosteroid treatment for at least 4 weeks prior to the first dose of study drug(s).
2. Active autoimmune diseases or history of autoimmune diseases that may relapse

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

   a. Controlled type 1 diabetes
   b. Hypothyroidism (provided it is managed with hormone replacement therapy only)
   c. Controlled celiac disease
   d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
   e. Any other disease that is not expected to recur in the absence of external triggering factors
3. Any active malignancy ≤ 2 years before the first dose of study drug(s), except for the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast)
4. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before administration of study drug

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

   a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
   b. Topical, ocular, intra-articular, intranasal, or inhalational corticosteroid with minimal systemic absorption
   c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)
5. With uncontrolled diabetes or > Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management
6. With significant pulmonary disease (ie, chronic obstructive pulmonary disease [COPD], emphysema or chronic bronchitis) or with history of interstitial lung disease, noninfectious pneumonitis or uncontrolled diseases including pulmonary fibrosis, acute lung diseases, etc.
7. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc. Note: antiviral therapy is permitted for patients with hepatocellular carcinoma
8. A known history of HIV infection
9. A known history of HBV or HCV infection, except for patients with HCC

Note: For patients with HCC only: patients with detectable HBsAg or detectable HCV antibody at screening must be excluded unless their HBV DNA titers < 500 IU/mL or HCV RNA polymerase chain reaction test is negative respectively. In addition, patients with detectable HBsAg or detectable HBV DNA should be managed per treatment guidelines. Patients receiving antivirals at Screening should have been treated for > 2 weeks prior to the first dose of study drug (s) and should continue treatment for 6 months after the last dose of study drug(s).

10. Any major surgical procedure ≤ 28 days before the first dose of study drug(s)
11. Prior allogeneic stem cell transplantation or organ transplantation
12. Any of the following cardiovascular criteria:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug(s)
    b. Symptomatic pulmonary embolism ≤ 28 days before the first dose of study drug(s)
    c. Any history of acute myocardial infarction ≤ 6 months before the first dose of study drug(s)
    d. Any history of heart failure meeting New York Heart Association Classification (NYHA) III or IV (Appendix 6) ≤ 6 months before the first dose of study drug(s)
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug(s)
    f. Any history of cerebrovascular accident ≤ 6 months before the first dose of study drug(s)
    g. Uncontrolled hypertension: systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg despite anti-hypertension medications ≤ 28 days before the first dose of study drug(s)
    h. Any episode of syncope or seizure ≤ 28 days before the first dose of study drug(s)
13. A history of severe hypersensitivity reactions to other mAbs
14. Has received any chemotherapy, radiotherapy, immunotherapy (eg, interleukin, interferon, thymoxin, etc.) or any investigational therapies within 28 days or 5 half-lives (whichever is shorter) of the first study drug (s) administration.

    Has received any Chinese herbal medicine or Chinese patent medicines used to control cancer within 14 days of the first study drug administration
15. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
16. Was administered a live vaccine ≤ 4 weeks prior to study drug administration

    Note: seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines, and are not allowed
17. Underlying medical conditions, laboratory abnormality, or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or adverse events; or insufficient compliance during the study according to investigator's judgement
18. Concurrent participation in another therapeutic clinical trial
19. Received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulation pathways).

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. BGB-A333

BGB-A333 is a mAB formulated for IV injection in a single-use glass vial (USP type I), containing a total of 450 mg antibody in 18 mL of isotonic solution. BGB-A333 has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

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

The study drug must be kept at the temperature condition as specified on the label. BGB-A333 drug product does not contain any preservatives and must be stored at temperatures between 2 °C and 8°C. Protect from light until time to use. Observations to date support drug stability for at least 18 months under this storage condition.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the IB for other details regarding BGB-A333.

5.1.2. Tislelizumab

Tislelizumab is a mAB formulated for IV injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

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

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

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

5.2. Dosage, Administration, and Compliance

Planned dose levels for BGB-A333 and tislelizumab are provided in Table 3. All patients will be monitored continuously for AEs. Treatment modifications (eg, dose delay or discontinuation) will be based on specific laboratory and AE criteria, as described in Section 5.5.

Table 3. Planned Dose Levels for BGB-A333 and Tislelizumab

Study Drug	Dose	Frequency of Administration	Route of Administration	Duration of Treatment
BGB-A333	450 mg, 900 mg, 1350 mg, 1800 mg (optional), 2250 mg (optional)	Every 3 weeks (additional dose levels or dosing regimens may be explored)	Intravenous	See Section 3.3.2
Tislelizumab	200 mg	Every 3 weeks (additional dose levels or dosing regimens may be explored)	Intravenous	See Section 3.3.2

The initial dosing regimen for BGB-A333 and tislelizumab (in Phase 1B and Phase 2B only) will be administered on D1 of each 21-day cycle (ie, Q3W). Other dosing regimens may be explored based on safety, PK and antitumor activities observed in dose levels completed.

BGB-A333 and tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein-binding filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual. BGB-A333 and tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

For BGB-A333 monotherapy (Phase 1A and Phase 2A), on C1D1, C2D1 and C3D1, the infusion of BGB-A333 will be delivered over 60 (± 5) minutes. After infusion of BGB-A333, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If BGB-A333 infusion is well tolerated in the first three cycles, on C4D1 and subsequent cycles, BGB-A333 may be administered over 30 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 30 minutes in an area with resuscitation equipment and emergency agents.

The infusion rate may be decreased or infusion may be stopped in the event of infusion-related reactions. See Section 8.7 for details.

For BGB-A333 and tislelizumab combination arms (Phase 1B and Phase 2B), on C1D1 and C2D1, Tislelizumab will be administered first over 60 (± 5) minutes followed by the administration of BGB-A333 over 60 (± 5) minutes. After infusion of BGB-A333, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of tislelizumab and BGB-A333 are well tolerated in the first two cycles, on C3D1, tislelizumab may be administered over 30 (± 5) minutes followed by the administration of BGB-A333 over 60 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 120 minutes in an area with resuscitation equipment and emergency agents.

If infusions of tislelizumab and BGB-A333 are well tolerated in the first three cycles, on C4D1 and subsequent cycles, tislelizumab may be administered over 30 (± 5) minutes followed by the administration of BGB-A333 over 30 (± 5) minutes and, after infusion of BGB-A333, patients must be monitored for at least 30 minutes in an area with resuscitation equipment and emergency agents.

The infusion rate may be decreased or infusion may be stopped in the event of infusion-related reactions. See Section 8.7 for details.

Table 4. Administration of BGB-A333 and Tislelizumab and Monitoring Time

Cycle	BGB-A333 monotherapy	BGB-A333 and Tislelizumab combination
C1D1 and C2D1	• BGB-A333 infusion over 60 (± 5) minutes • Patient monitoring for at least 120 minutes	• Tislelizumab infusion over 60 (± 5) minutes • BGB-A333 infusion over 60 (± 5) minutes • Patient monitoring for at least 120 minutes
C3D1	• BGB-A333 infusion over 60 (± 5) minutes; • Patient monitoring for at least 120 minutes	• Tislelizumab infusion over 30 (± 5) minutes • BGB-A333 infusion over 60 (± 5) minutes • Patient monitoring for at least 120 minutes
C4D1 onwards	• BGB-A333 infusion over 30 (± 5) minutes • Patient monitoring for at least 30 minutes	• Tislelizumab infusion over 30 (± 5) minutes • BGB-A333 infusion over 30 (± 5) minutes • Patient monitoring for at least 30 minutes

Abbreviations; C1D1 = Cycle 1, Day 1; C2D1 = Cycle 2, Day 1; C3D1 = Cycle 3, Day 1; C4D1 = Cycle 4, Day 1
* The infusion rate may be decreased or infusion may be stopped in the event of infusion-related reactions. See Section 8.7 for details.

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of infusion-related reactions and irAEs are provided in detail in Section 5.4, Section 8.7.1, and Appendix 8.

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

5.3. Overdose of Tislelizumab and Incorrect Administration of BGB-A333

Any overdose of tislelizumab (defined as ≥ 600 mg in a 24-hour period) or incorrect administration of BGB-A333 should be noted in the patient's chart and on the study drug administration electronic case report form (eCRF).

Adverse events associated with an incorrect administration of study drug will be recorded on the adverse event eCRF. If an incorrect administration of study treatment takes place and adversely affects the patient's safety, the sponsor or designee is required to be notified within 24 hours of awareness via SAE reporting process described in Section 8.6.2. Supportive care measures should be administered as appropriate.

5.4. Dose Delay and Modification

5.4.1. Dose Modification

There will be no dose reduction for BGB-A333 or tislelizumab within a given patient in this study.

In Phase 1A (BGB-A333 monotherapy), if patients progress on BGB-A333 without other safety concerns, these patients may be treated with a higher dose of BGB-A333 that is deemed to be well tolerated by SMC. The decision to modify the dose of BGB-A333 must be discussed with the sponsor's medical monitor and documented in the study records.

In Phase 1A and Phase 2A (BGB-A333 monotherapy), if patients progress on BGB-A333 monotherapy without other safety concerns, these patients may receive combination of BGB-A333 and tislelizumab at doses that are deemed to be well tolerated by SMC. The decision to add tislelizumab to patients treated with BGB-A333 alone must be discussed with the sponsor's medical monitor and documented in the study records.

5.4.2. Dose Delay

Dose delays or interruptions less than 12 weeks will be permitted. The tumor assessment schedule will not be altered even if the administration of study drug(s) is delayed.

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

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to study drug(s) and requires a dose to be withheld. The patients should resume study drug treatment as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) within 12 weeks after last dose of study drug(s).

If the patient is unable to resume study drug treatment within 12 weeks after the last dose of study drug, then the patient should be discontinued from study drug treatment.

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

Dose modification related to irAEs and infusion-related reactions are described in Appendix 8 and Section 8.7.1, respectively.

6. PRIOR AND CONCOMITANT THERAPY

6.1. Concomitant Therapy

6.1.1. Permitted Concomitant Medications and Therapy

Most concomitant medications and therapies deemed necessary in keeping with the local standards of medical care at the discretion of the investigator for supportive care (eg, anti-emetics, anti-diarrheals) and in a patient's interest are allowed. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids.

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

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 8) and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next administration of study drug(s). The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to enrollment and at a stable dose. Bisphosphonates are permitted during the trial only for a nonmalignant indication.

HBV or HCV treatment should be according to local guidelines. Anti-viral therapy given for prevention of HBV reactivation must be started 2 weeks prior to first dose of study drug(s) and continued for 6 months after the last dose of study drug(s).

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

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

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
- The case is discussed with sponsor medical monitor, who agrees that the conditions required to receive palliative radiation are met

Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

6.2. Prohibited or Restricted Concomitant Medications and Therapy

The following medications are prohibited or restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat or control a drug-related AE or for short-term use as prophylactic treatment
- Any concurrent antineoplastic therapy (ie, 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 except for palliative radiation therapy described in Section 6.1.1
- Live vaccines within 28 days prior to the first dose of study drug(s) and 60 days following the last dose of study drug(s)
- Herbal remedies with immune-stimulating properties (ie, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (ie, hypericin). Patients must notify the investigator of all herbal remedies used during the study
- For patients with HCC only, patients should avoid alcohol completely and should avoid other addictive drugs during the study. Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored. Patients must notify the investigator of all concurrent medications used during the study
- Interferon-based therapy for either HBV or HCV is not permitted during the study

6.3. Potential Interactions Between the Study Drugs and Concomitant Medications

The potential for drug-drug interaction between the study drugs (BGB-A333 and tislelizumab) and small-molecule drug products is very low, given BGB-A333 and tislelizumab are therapeutic mAB. Because BGB-A333 and tislelizumab are expected to be degraded into amino acids and recycle into other proteins, it is unlikely to have an effect on drug metabolizing enzymes or transporters.

7. STUDY ASSESSMENTS AND PROCEDURES

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

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

7.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose of study drug(s). Patients who agree to participate will sign the ICF prior to undergoing any screening procedure (refer to Appendix 1 for details). Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function test (refer to Appendix 1 for details). Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess patient eligibility according to the latest screening assessment results.

Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of the study drug(s) 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 at Screening as well as throughout the study, refer to Safety Assessments (Section 7.3), Tumor and Response Evaluation (Section 7.4), Pharmacokinetic Assessment (Section 7.5) and Biomarkers (Section 7.6). The PK sampling schedule is shown in Appendix 1 (C-F).

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

7.1.1. Demographic Data and Medical History

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

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (ie, of childbearing potential or no childbearing potential); history of alcohol consumption and tobacco (ie, former or current or never); and all medications (eg, prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 30 days before the first dose of study drug(s).

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

7.1.2. Females of Childbearing Potential and Contraception

Childbearing potential is defined as being physiologically capable of becoming pregnant. Refer to Appendix 5 for contraception guidelines and definitions of "women of childbearing potential" and "no childbearing potential".

7.1.3. Informed Consent and Screening Log

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

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

7.1.4. Pulmonary Function Tests

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

7.2. Enrollment

7.2.1. Confirmation of Eligibility

The investigator will assess and the sponsor will confirm the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. Eligible patients must meet all inclusion criteria and patients who meet any of the exclusion criteria are not eligible to enroll. No eligibility waivers will be granted.

After a patient is screened and the investigator determines the patient is eligible for enrollment, study site personnel will complete a Treatment Authorization Packet and email it to the medical monitor or designee to approve the enrollment in writing. Study site personnel should ensure that a medical monitor's approval has been received before proceeding with study procedures.

7.3. Safety Assessments

7.3.1. Vital Signs

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

7.3.2. Physical Examinations

During the screening visit, a complete physical examination will be conducted including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory,

6) gastrointestinal, and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE v 4.03 and recorded on the Medical History eCRF with appropriate disease/condition terms.

At subsequent visits (or 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 adverse events on the Adverse Event eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.3.2.1. Ophthalmologic Examination

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist at Screening. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) captured as standard of care prior to obtaining written informed consent and within 28 days of the first dose of the study drug(s) may be used for the Screening evaluation. Patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment and a final assessment < 30 days (± 7 days) after the last dose of study treatment.

In addition, investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during study treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance (see Appendix 8).

7.3.3. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Appendix 3) will be assessed during the study.

7.3.4. Laboratory Safety Test

Local and/or central laboratory assessments on hematology, serum chemistry, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2.

If laboratory tests at screening are not performed within 96 hours prior to the administration of study drug(s) on C1D1, these tests should be repeated and reviewed within 72 hours before study drug(s) administration. Hematology and serum chemistry (including liver function tests) as specified in Appendix 2 should be performed weekly for the first 3 cycles and at the beginning of subsequent cycles. After Cycle 1, laboratory safety results should be reviewed within 72 hours before study drug administration.

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

In addition, the following tests will be conducted in this study:

- Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to administration of study drug(s). Urine or serum pregnancy tests will be performed Q3W or monthly during treatment and at Safety Follow-up. A serum pregnancy test must be performed if

the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or blood) must be completed and recorded before administration of study drug(s) at each cycle.

- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the Safety Follow-up Visit.

7.3.5. Electrocardiograms

A centralized ECG laboratory may be used in this study in selected study sites. Calibrated ECG machines will be provided to these sites and ECG collected from these sites will be reviewed centrally. In other sites, local ECG machines will be used.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's study file at the site.

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

At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval.

7.3.6. Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03 (NCI-CTC, June 2010). Characterization of toxicities will include severity, duration, and time to onset.

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

7.3.7. Hepatitis B and C Testing

In patients with HCC only, hepatitis serology and viral load will be tested at Screening. Patients who have detectable HBsAg or HCV antibody at screening must not be enrolled unless HBV DNA titers < 500 IU/mL or HCV RNA polymerase chain reaction test is negative respectively. Patients who have detectable HBV DNA at Screening will perform the viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc), at EOT visit, and when clinically indicated.

In other patients, blood samples for hepatitis serology and viral load will be collected at Screening and may be tested if patients have hepatic AE (Grade ≥3) during the study. Testing will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

7.4. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to the first study treatment. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug(s) may be used for the purposes of screening rather than repeating the standard of care tests. During the study, tumor imaging will be performed approximately every 9 weeks (± 7 days) (for Q3W dosing) or every 8 weeks (± 7 days (for Q2W or Q4W dosing) in the first year and thereafter approximately every 12 weeks (± 7 days).

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

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

- Imaging of the brain (MRI or CT) at baseline (≤ 28 days of the first dose of study drug(s)) is required for all patients
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan
- Bone scans (Technetium-99m [TC-99m]) or sodium fluoride PET (NaF-PET) should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen on CT or MRI scans afterwards, TC-99m or NaF-PET bone scans should be conducted when a CR is suspected in target lesion. In addition, TC-99m or NaF-PET bone scans may be conducted when progression in bone is suspected
- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at Screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used

Tumor response will be assessed by the investigators using RECIST v1.1 (see Appendix 9). Additional information on new lesions will be collected according to iRECIST (see Appendix 10) and sponsor will derive tumor response using iRECIST as an exploratory assessment. The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

For immune therapies such as BGB-A333 and tislelizumab, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients may continue treatment with study drug(s) until PD is confirmed by repeated imaging at least 4 weeks later but not exceeding 8 weeks from the date of initial

documentation of PD. The following criteria must be met in order to continue study drug treatment in patients with suspected pseudoprogression:

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

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

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

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

7.5. Pharmacokinetic Assessment and Antidrug Antibody Testing

BGB-A333 and tislelizumab may elicit an immune response. Patients with signs of any potential immune response will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study (see Appendix 1 [C-F]). An optional PK sample may be collected if a patient experiences an adverse event that requires understanding of drug exposure at the time of event.

The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al 2008; Worobec and Rosenberg 2004a; Worobec and Rosenberg 2004b) to characterize ADA responses to BGB-A333 and tislelizumab in support of the clinical development program.

The following assessments will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to BGB-A333 and tislelizumab using a validated immunoassay.
- PK assay: serum samples will be assayed for BGB-A333 and tislelizumab concentration with use of a validated immunoassay.

Shipping, storage, and handling of samples for the assessment of BGB-A333 and tislelizumab PK and ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

7.6. Biomarkers

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

Archival tumor tissues (formalin-fixed paraffin-embedded block [FFPE] with tumor tissue or approximately 15 [≥7] unstained slides) need to be sent to central laboratory for central immunohistochemistry assay of PD-L1 status. In addition to PD-L1 expression, other exploratory predictive biomarkers, such as TIL assessment, tumor mutation load and gene expression profiling, that are related to response or clinical benefit of BGB-A333 and tislelizumab may also be evaluated. If no archival samples are available, a fresh tumor biopsy at baseline is highly recommended.

For fresh biopsy specimens, acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

The optional biopsy will also be taken at the end of treatment visit for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples, the resistance mechanism will be explored by NGS-based gene sequencing. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient informed consent is required before obtaining fresh tumor biopsies.

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

Around 5 mL peripheral blood samples will be collected at specified times in Phase 1 as described in the schedule of assessments to be used for the evaluation of PD measurements, such as, but not limited to, effects of BGB-A333 on immune cell subtypes.

7.7. Safety Follow-Up Visit

Patients will return for a follow-up visit at approximately 30 (±7) days after last dose of the study drug(s). In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications at 60 and 90 days (±14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy. SAEs and irAEs are collected up to 90 days. Beyond 90 days, investigators should report any SAEs or irAEs that are believed to be related to study drug(s) if they become aware of them. Patients who discontinue study drug(s) due to a drug-related AE will be followed until the resolution of the AE (to Grade 0 to Grade 1, baseline, stabilization) or initiation of a new treatment, whichever comes first.

Any end-of-treatment (EOT) visit at which a response assessment showed PD, resulting in patient discontinuation, may be used as the Safety Follow-up visit, if appropriate. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.4.

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

7.8. Visit Windows

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date, with subsequent visits conducted according to the original schedule calculated from Cycle 1 Day 1.

7.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or investigator's request and may include review of AE, concomitant medications and procedures; assessments of vital signs, physical examination, ECOG performance status, laboratory safety tests, ECG, and radiographic assessments.

The date and reason for the unscheduled visit must be recorded in the source documentation.

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

7.10. Site Closure

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

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

8. SAFETY MONITORING AND REPORTING

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

8.1. Risks Associated with BGB-A333 and Tislalizumab

BGB-A333 and tislelizumab are investigational agents that are currently in clinical development. No clinical information is available for BGB-A333 whereas limited safety data for tislelizumab are available in patients and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical studies of BGB-A333 and non-clinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 8.7.

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

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies of BGB-A333 and tislelizumab, clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, and patients who have received a live vaccine within 28 days before administration of study drug(s) are excluded from the study (see Section 4.2).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all adverse events, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed prior to the start of each cycle.

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

Serum samples will be drawn for determination of ADAs to BGB-A333 in all patients and to tislelizumab in patients for Phase 1B and Phase 2B only. Administration of study drug(s) will be performed in a setting

where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2).

All AEs will be recorded during the study (AE from the time of the first dose of study drug(s) and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing adverse events considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

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

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

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

8.3. Adverse Events

8.3.1. Definitions and Reporting

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

Examples of AEs include:

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

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

8.3.2. Assessment of Severity

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

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

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

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should refer to the Investigator’s Brochures of BGB-A333 and tislelizumab in the determination of his/her assessment.

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

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

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

An AE should be considered "related" to study drug if any of the following are met:

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

An AE should be considered "unrelated" to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the product and the onset on the AE (eg, the AE occurred either before, or too long after administration of the product for it to be considered product-related)
- A causal relationship between the product and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE)

8.3.4. Following Adverse Events

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

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

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

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

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

8.3.5. Laboratory Test Abnormalities

Only abnormal laboratory findings (eg, serum chemistry, complete blood count (CBC), coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE

(as defined in Section 8.3) or an SAE (as defined in Section 8.4). Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

8.4. Definition of a Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

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

8.5. Suspected Unexpected Serious Adverse Reaction

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

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

8.6.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study drug or initiation of new anticancer therapy, whichever occurs first. Immune-related adverse events (serious or non-serious) should be reported until 90 days after the last dose of study drug(s), regardless of whether or not the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to study drug(s), at any time after treatment discontinuation.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

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

Table 5. Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-Up Report	Documentation Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE report	As expeditiously as possible	SAE report

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

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.6.1. The SAE report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality at the time of the initial report as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1 and Section 8.6.2.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

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

All SUSARs (as defined in Section 8.5), will be submitted to all applicable regulatory authorities and investigators for tislelizumab and BGB-A333 studies.

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

8.6.3. Eliciting Adverse Events

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

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

8.6.4. Recording Disease Progression

Disease progression is expected in this study population, and the term “disease progression” should not be reported as an AE term. When disease progression is identified, the AE that is associated with the disease progression should be reported as the AE term. For instance, for a patient who has a seizure that is determined to be associated with a brain metastasis, the term “seizure” should be recorded as the AE instead of disease progression or brain metastasis. Deaths that are assessed by the investigator as likely due to disease progression should be recorded in the eCRF. The term “death” should not be reported as an AE or SAE term, but rather as an outcome of an event.

8.6.5. Recording Deaths

When recording a death as an SAE, the symptomatic deterioration and AE that caused or contributed to fatal outcome should be recorded in the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death."

8.6.6. Recording 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 BGB-A333, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

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

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

8.6.7. Recording Post-Study Adverse Events

A poststudy AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period that is defined in Section 8.6.1.

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

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

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

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

- BGB-A333 and tislelizumab IB

8.6.9. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 or anti-PD-L1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 8.7.3) should be classified as irAEs and identified as such in the eCRF AE page until Day 90 after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential irAEs appears in Section 8.7.3, Table 7. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 8.

8.7. Management of AE of Special Interest

As a routine precaution, after infusion of BGB-A333 alone or in combination with tislelizumab, patients must be monitored in an area with resuscitation equipment and emergency agents. The infusion time and monitoring time are shown in Table 4.

The management of infusion-related reactions, severe hypersensitivity reactions and irAEs according to the NCI-CTCAE criteria are outlined below.

8.7.1. Infusion-Related Reactions

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

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

Table 6. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for BGB-A333 and Tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.

Table 6. Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

Grade 3 – severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended

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

Once the BGB-A333 and/or tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions with premedication. If the patient has a second infusion-related reaction (Grade ≥ 2) on the slower infusion rate, infusion should be discontinued and the patient should be withdrawn from BGB-A333 and/or tislelizumab treatment.

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

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

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

In the event of a systemic anaphylactic/anaphylactoid reaction (typically manifested within minutes following administration of the drug/antigen, and characterized by: respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent

respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea), the infusion must be immediately stopped and the patient discontinued from the study.

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

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

8.7.3. Immune-Related Adverse Events

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

A list of potential irAEs is shown below in Table 7. All conditions similar to those listed should be evaluated in patients receiving BGB-A333 alone or in combination with tislelizumab to determine whether they are immune-related.

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

Table 7. Immune-Related Adverse Events

Body System Affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet's syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism, eg, fatigue, weakness, weight gain; insulin-dependent diabetes mellitus; 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

Recommendations for managing irAEs are detailed in Appendix 8.

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 the any event at the same or higher severity grade with re-challenge should permanently discontinue treatment.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. Data will be listed and summarized using SAS® Version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina) per sponsor agreed reporting standards, where applicable. Details of the statistical analyses will be included in a separate Statistical Analysis Plan (SAP).

Efficacy and safety data will be summarized by phase and tumor type where appropriate.

9.1. Statistical Analysis

9.1.1. Randomization Methods

Not applicable.

9.1.2. Analysis Populations

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

Efficacy Evaluable Population includes all dosed patients who have evaluable disease at baseline, and at least 1 evaluable post-baseline tumor response assessment unless any clinical PD or death occurred before the first post-baseline tumor assessment.

DLT Evaluable Population for BGB-A333 monotherapy includes patients who received at least two-thirds (67%) of the assigned dose of BGB-A333 during the DLT observation period and had sufficient safety evaluation or patients who experienced DLT within DLT observation period.

DLT Evaluable Population for BGB-A333 and tislelizumab combination includes patients who received at least two-thirds (67%) of the assigned dose of BGB-A333 and tislelizumab during the DLT observation period and had sufficient safety evaluation or patients who experienced DLT within DLT observation period.

The PK analysis population includes all patients with valid PK sampling after treatment with study drug(s).

9.1.3. Patient Disposition

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

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

9.1.4. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer

diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include prior number of systemic treatment, gender, ECOG, country, race, and metastatic site.

9.1.5. Prior and Concomitant Medications

Concomitant medications will be assigned an 11-digit code using the World Health Organization (WHO) Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 and 90 days (±14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

Safety and MTD/RP2D determination are the primary objectives in the Phase 1 part. Evaluation of ORR of BGB-A333 alone and in combination with tislelizumab in the selected tumor types is the primary objective in Phase 2 part.

The efficacy per RECIST 1.1 (ie, ORR, DOR, PFS, and DCR) will be summarized to evaluate antitumor activities of BGB-A333 alone or in combination with tislelizumab in patients with measurable disease at baseline. Efficacy summary will be provided by tumor type.

9.2.1. Primary Efficacy Analysis in Phase 2

ORR and its 95% CI will be summarized in the Safety and Efficacy Evaluable Populations. ORR in Phase 2 will be presented by tumor type.

9.2.2. Secondary Efficacy Analysis in Phase 2

PFS will be estimated using the Kaplan-Meier (KM) method. The median PFS and landmark PFS at every 3 months will be calculated and presented with 2-sided 95% CIs. PFS censoring rule will follow FDA Guidance. The PFS censoring rule will follow *United States (US) Food and Drug Administration (FDA) Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics* (2007) (FDA Guidance for Industry 2007).

DOR will be analyzed in the responders.

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

DCR will be analyzed similarly to ORR in the Safety and Efficacy Evaluable Populations.

Waterfall plots of maximum tumor shrinkage per patient will be presented.

9.2.3. Exploratory Efficacy Analysis

[redacted]

9.3. Safety Analyses

Safety will be determined by the spontaneous reporting of adverse events and by laboratory values (hematology, serum chemistry, coagulation, and urinalysis). Vital signs, physical examination and ECG findings will also be used in determining the safety profile. The severity of adverse events will be graded according to the CTCAE v4.03. The incidence of DLT events, treatment-emergent AEs (TEAEs) will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Safety data will be summarized in the Safety Population, and by study phase or tumor type if necessary.

9.3.1. Extent of Exposure

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

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation due to AEs will be summarized for each study drug.

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

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be coded to MedDRA (Version 18.1 or higher) lower level term, preferred term and primary system organ class (SOC).

DLT will be summarized at each dose cohort in Phase 1A and Phase 1B.

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

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade per NCI-CTCAE v.4.03 within an

SOC and PT, even if the patient experienced more than 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. TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. SAEs, deaths, TEAE with ≥ Grade 3 severity, irAE, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, serum chemistry, urinalysis) values will be evaluated for each laboratory parameter by patient. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n[%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

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

9.3.4. Vital Signs

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

9.3.5. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.4. Pharmacokinetic Analysis

In Phase 1, BGB-A33 PK variables (eg, C_{max}, T_{max}, trough serum concentration [C_{trough}], AUC, Cl, and V_d) will be calculated as appropriate using noncompartmental methods and summary statistics will be provided. BGB-A333 serum concentration data and PK parameters will be tabulated and summarized for each cycle at which pharmacokinetics are to be measured in Phase 1 and Phase 2. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate. Mean serum concentrations will also be plotted against time for each dose level. Additional PK analyses may be conducted as appropriate.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. Results of such analyses may be reported separately from the CSR.

Tislelizumab serum concentration data will be tabulated and summarized for each cycle at which PK are to be measured.

9.5. Immunogenicity Analyses

Samples to assess anti-BGB-A333 antibodies as well as anti-tislelizumab antibodies will be collected only in patients who receive the treatment.

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

9.6. Other Exploratory Analyses

[redacted]

9.7. Sample Size Consideration

The study plans to enroll approximately 58 to 168 patients.

- Phase 1A (BGB-A333 dose escalation): Approximately 12 to 30 patients with advanced solid tumors in 3-5 dose levels or dosing regimens per modified 3+3 design.
- Phase 1B (BGB-A333 and tislelizumab combination): Approximately 6 patients with advanced solid tumors in one combination dosing regimen. An additional 12 patients may be enrolled to test different dosing regimens.
- Phase 2A (BGB-A333 dose expansion): Approximately 20 patients with UC. Additional 20-40 patients with other tumor types (to be defined in future protocol amendments based upon emerging data) may be enrolled.
- Phase 2B (BGB-A333 and tislelizumab combination dose expansion): Approximately 20 patients with UC. An additional 20-40 patients with other tumor types (to be defined in future protocol amendments based upon emerging data) may be enrolled.

In Phase 2, approximately 20 patients per cohort will be enrolled to evaluate the preliminary efficacy. No formal hypothesis testing will be performed in the efficacy evaluation. With 20 patients, the probabilities of observing at least one responder under different underlying ORR assumptions are summarized in Table 8, indicating the proposed sample size is adequate to detect any preliminary anti-cancer activities of the treatment. The 95% CIs of the ORR estimate when observing 1 to 6 responders are included in Table 9, depicting the precision achieved with 20 patients.

Table 8. Time Probabilities of Observing at least One Responder in 20 Patients under Various ORR Assumptions

ORR	**0.10**	**0.20**	**0.30**	**0.40**
Probability (observing ≥ 1 responder)	0.88	0.99	> 0.99	> 0.99

Table 9. 95% CI (%) when Observing 1 to 6 Responders in 20 Patients

# of responders	**1**	**2**	**3**	**4**	**5**	**6**
95% CI	(0.1, 24.8)	(1.2, 31.7)	(3.2, 37.9)	(5.7, 43.7)	(8.7, 49.1)	(11.9, 54.3)

9.8. Interim Analyses

Not applicable.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Safety Monitoring Committee

SMC will be established and includes both the sponsor and at least 2 investigators. The SMC will review all available safety, efficacy, PK, and exploratory data and make recommendation on dose escalation, dose modification, and dose selection for Phase 1B and Phase 2.

10.2. Communication

Sponsor plans to have regular communications with all study sites (study investigators and coordinators) regarding:

- Study enrollment status
- Any significant safety findings
- Decisions on dose escalation
- Considerations for protocol amendments

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

In accordance with International Council on Harmonisation (ICH) GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the 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.

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

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

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

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

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

This study will be conducted in full conformance 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 individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

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

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

13.2.1. Protocol Amendments

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

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

13.3. Informed Consent

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

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

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

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

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

13.4. Patient and Data Confidentiality

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

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

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

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

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

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient and accurate financial information, in accordance with local regulations to allow the sponsor to submit complete disclosure or certification the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into the EDC system.

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

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

14.1.2. Data Management/Coding

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

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

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

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher. Concomitant medications and medical history will be coded using the World Health Organization Drug Dictionary.

14.2. Data Integrity

Due to the open-label design of the study, access to the unblinded patient level clinical data in the Electronic Data Capture (EDC) system will only be assigned to predefined study personnel. Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias, or share such outputs or the unblinded data from the EDC system with other functions/persons who do not have access to the EDC.

Although the trial is open-label, analyses or summaries generated by treatment assignment and actual treatment received will be limited and documented.

14.3. Study Records Retention

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

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

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

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

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

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

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

14.4. Protocol Deviations

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

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

14.5. Publication and Data Sharing Policy

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

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

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

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years
- No such communication, presentation, or publication will include BeiGene's confidential information
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor at least 30 days prior to submission. This allows the sponsors to protect confidential information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement

14.6. Study and Study Center Closure

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

- Return of all study data to the sponsor

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

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

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

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

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

14.7. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

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

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

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

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel

- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a patient
- Study results which may be published as described in Section 14.5

If a written contract for the conduct of the study (which includes confidentiality provisions inconsistent with this section) is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Appendix 1A. Schedule of Assessments

Assessment	Screening[1]	Treatment Period			Safety Follow-up Visit[4]	Safety Follow-up Phone Call[4]
		Cycles 1 to 3[2]	Cycle 4 and Subsequent Cycles	End of Treatment Visit[3]		
Days (window)	**-28 to -1**	**1 (± 3 for C2D1 or C3D1), 8 (± 3), 15 (± 3)**	**1 (± 3)**	**0 to 7 days after last dose**	**30 (± 7) days after last dose**	**60 (± 14), 90 (± 14) days after last dose**
Informed consent[1]	x					
Inclusion/exclusion criteria	x					
Demographic/Medical history/Prior medications[5]	x					
Vital signs/Height/Weight[6]	x	x (Day 1 only)	x	x	x	
Physical examination[7]	x	x (Day 1 only)	x	x		
ECOG performance status[8]	x	x (Day 1 only)	x	x	x	
12-lead ECG[9]	x	x (C1D1, C1D8, C1D15 and C2D1 only)	x (C5D1 only and as clinically indicated)	x	x	
Adverse events[10]	x	x	x	x	x	x
Concomitant medications[11]	x	x	x	x	x	x
Hematology[12]	x	x	x	x	x	
Serum chemistry (including CK and CK-MB)[12]	x	x	x	x	x	
Coagulation parameters[13]	x	x (Day 1 only)	x	x	x	
Urinalysis[14]	x	as clinically indicated			x	

Assessment	Screening[1]	Treatment Period			Safety Follow-up Visit[4]	Safety Follow-up Phone Call[4]
		Cycles 1 to 3[2]	Cycle 4 and Subsequent Cycles	End of Treatment Visit[3]		
Days (window)	**-28 to -1**	**1 (± 3 for C2D1 or C3D1), 8 (± 3), 15 (± 3)**	**1 (± 3)**	**0 to 7 days after last dose**	**30 (± 7) days after last dose**	**60 (± 14), 90 (± 14) days after last dose**
Pregnancy test[15]	x	before study drug administration at each cycle			x	
Thyroid function test[16]	x		x every 3 cycles (Day 1 of C4, C7, C10, etc.)		x	
HBV/HCV tests[17]	In patients with HCC only	every 4 cycles in patients with detectable HBV DNA at Screening or as clinically indicated in all patients			Only in patients with detectable HBV DNA at Screening	
Pulmonary function test[18]	x	as clinically indicated				
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[19]	x	every 15 weeks (± 7 days)		within 30 days after the last dose		
Tumor assessment[20]	x	in the first year, every 9 weeks (for Q3W dosing) or every 8 weeks (for Q2W or Q4W dosing). Every 12 weeks thereafter			x	
Bone scan[21]	x	as clinically indicated				
Archival tumor tissues[22]	x					
Fresh tumor tissues (optional)[23]	x			x		
BGB-A333 administration (Phase 1A)[24]		x	x			
Tislelizumab and BGB-A333 administration (Phase 1B)[25]		x	x			
Pharmacodynamic Blood Biomarkers (**Phase 1 only**)[26]		x (C1D1, C1D15, C2D1 and C3D1 only)				

Abbreviations: AE = adverse event; C1D1 = Cycle 1, Day 1; C1D8 = Cycle 1, Day 8; C1D15 = Cycle 1, Day 15; C3D1 = Cycle 3, Day 1; C5D1 = Cycle 5, Day 1; CK = Creatine kinase; CK-MB = Creatine kinase-cardiac muscle isoenzyme; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; HBV = hepatitis B virus; HCV = hepatitis C virus; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; x = to be performed.

1. **During Screening,** written informed consent must be signed before performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1 Day 1 may be used for screening assessments rather than repeating such tests.
2. **In Cycles 1 to 3**, patients will receive study drug on Day 1 and return to study sites for assessments on Day 8. In addition, patients on Q3W, Q4W or longer intervals will return to study sites on Day 15.
3. **The End of Treatment Visit** is conducted when the investigator determines that study drug(s) will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, tests need not be repeated. Tumor assessment is not required at the End of Treatment Visit provided that less than 6 weeks have passed since the last assessment.
4. **The Safety Follow-up Visit and Phone calls:** Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow up Visit (to occur within 30 days [± 7 days] after the last dose of study drug or before the initiation of a new anticancer treatment, whichever occurs first. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications (if appropriate, ie, associated with an irAE or is a new anticancer therapy) at 60 days (±14 days) and 90 days (±14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the Investigator as stable, the patient is lost to follow-up, or the patient withdraws consent.
5. **Demographic data, medical history and prior medications** will be collected during screening (see Section 7.1.1 for details).
6. **Vital signs** collected on study include temperature, pulse, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. In the first cycle, vital signs should be collected within 60 minutes before the infusion of the study drug(s), and within 30 minutes after the infusion of the study drug(s). In the subsequent cycles, vital signs should be collected within 60 minutes before infusion and as clinically indicated. Height and weight should only be measured and recorded at screening only.
7. **Complete physical examination** including an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems is required to be performed at Screening. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations will be performed.
8. **ECOG Performance Status** (Appendix 3) will be assessed at Screening, Day 1 of each treatment cycle, EOT visit and the Safety Follow-up Visit.
9. **12-lead ECG** will be collected during screening, on C1D1, C2D1 and C5D1 at approximately 30 min before and approximately 30 min after dosing of BGB-A333. In addition, 12-lead ECG will be collected any time on C1D8, C1D15 (only in Q3W or longer dosing intervals), at EOT and the Safety Follow-up visits, and as clinically indicated. At each time point, 3 consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTcF interval. When coinciding with blood draws, ECG assessment should be performed prior to blood draws. Patients should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings.
10. **Adverse events** will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03.
11. **All concomitant medication** received within 30 days before the first dose of study treatment, 30 days after the last dose of study treatment, and at 60 or 90 days of follow up (if appropriate, ie, associated with a new adverse event or is a new anticancer therapy) should be recorded.
12. **Hematology and serum chemistry** as specified in Appendix 2 should be performed at screening and weekly for the first 3 cycles and at the beginning of subsequent cycles, EOT visit, Safety Follow-up visit and when clinically indicated**.** If these tests at screening are not performed within 96 hours prior to the administration of study drug(s) on C1D1, these tests should be repeated and reviewed within 72 hours before study drug(s) administration. After Cycle 1, test results should be reviewed within

72 hours before study drug administration. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
CK and CK-MB will be conducted at Screening, scheduled visits during the first 3 treatment cycles, and all pre-dose assessments from Cycle 4 onward, EOT visit, Safety Follow-up and when clinically indicated. If CK-MB fractionation is not available, troponin I and/or troponin T should be assessed instead.

13. **Coagulation tests** as specified in Appendix 2 are required at Screening, Day 1 of each treatment cycle, EOT visit, the Safety Follow-up Visit and as clinically indicated.
14. **Urinalysis** as specified in Appendix 2 will be conducted at Screening and the Safety Follow-up Visit and as clinically indicated.
15. **Serum pregnancy test** (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to administration of study drug(s). **Urine or serum pregnancy tests** will be performed before study drug administration at each cycle and at Safety Follow-up. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or serum) must be completed and recorded before administration of study drug(s) at each cycle.
16. **Thyroid function tests** include analysis of free T3, free T4 and TSH. Testing will be performed at Screening and every three cycles thereafter (eg, Cycles 4, 7, 10, etc.), and at the Safety Follow-Up Visit (see Section 7.3.4 for details).
17. **HBV/HCV tests**: In patients with HCC only, hepatitis serology and viral load will be tested at Screening. Patients who have detectable HBV DNA at Screening will perform the viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc), at EOT visit, and when clinically indicated. In other patients, blood samples for hepatitis serology and viral load will be collected at Screening and may be tested if patients have hepatic AE (Grade ≥ 3) during the study (see Section 7.3.7 for details).
18. **Pulmonary function test:** Patients who have a history of serious or severe pulmonary disease or are suspected to have serious or severe respiratory concurrent illness or exhibit significant respiratory symptoms should take a pulmonary function test at screening and as clinically indicated during study treatment (see Section 7.1.4 for details).
19. **Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests:** Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test for retinal examination) will be assessed by an appropriate specialist at Screening. Patients will undergo repeat assessments by an appropriate specialist approximately every 15 weeks (± 7 days) during study treatment after Cycle 1 and a final assessment within 30 days after the last dose of study treatment.
20. **Tumor imaging** will be performed within 28 days prior to C1D1 and while on study approximately every 9 weeks ± 7 days after C1D1 (for Q3W dosing) or every 8 weeks ± 7 days after C1D1 (for Q2W or Q4W dosing) in the first 12 months and approximately every 12 weeks ± 7 days thereafter. All measurable and evaluable lesions should be assessed and documented at the screening visit. Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. The same imaging technique should be used throughout the study for each patient. After the first documentation of response (CR or PR), confirmation of tumor response should occur at least 4 weeks (≥ 4 weeks) after the first response or at the next scheduled assessment time point. Progressive disease suspected as pseudoprogression needs to be confirmed by repeated imaging at least 4 weeks later but not exceeding 8 weeks from the date of initial documentation of PD. Patients who stop treatment prior to documentation of progressive disease will undergo repeated imaging for tumor response assessments (see Section 7.4 for details).
21. **Bone scan** is only required if disease is suspected or has been documented previously (see Section 7.4 for details).
22. **Archival tumor tissues** (formalin-fixed paraffin-embedded [FFPE] blocks or approximately 15 [≥7] unstained FFPE slides) will be collected if available.
23. **Fresh biopsy**: In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 28 days before Cycle 1 Day 1) is highly recommended. An optional biopsy will also be taken from patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanism (written inform consent is required prior to obtaining fresh tumor biopsies).
24. **BGB-A333 administration** (see Section 5.2 for details).
25. **Tislelizumab and BGB-A333 administration** (see Section 5.2 for details).
26. **PD biomarker (Phase 1 only):** Around 5 mL peripheral blood will be collected pre-dose at the following timepoints: C1D1, C1D15 (only for Q3W or longer dosing

intervals); C2D1, C3D1.

Appendix 1B. Pharmacokinetic and Immunogenicity Sampling Schedule for BGB-A333 (Q3W)

	Cycle	Week	Day	PK Assessment	ADA Assessment
Treatment Period	1	1	1	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***6-hr (± 2 hr) (Phase 1 only)*** ***Day 2 (± 2 hr) (Phase 1 only)*** ***Day 4 (± 2 hr) (Phase 1 only)*** ***Day 8 (Phase 1 only)*** ***Day 15 (Phase 1 only)***	Predose
	2	4	22	Predose (-60 min to predose) End of infusion (Within 30-min after EOI)	Predose
	5	13	85	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***Day 8 (Phase 1 only)*** ***Day 15 (Phase 1 only)***	Predose
	6	16	106	Predose (-60 min to predose) End of infusion (Within 30-min after EOI)	
	9	25	169	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	13	37	253	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	17	49	337	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	25	73	505	Predose (-60 min to predose)	Predose
	33	97	673	Predose (-60 min to predose)	Predose
	33 +8.	97 +24.		Predose every 6 months after	Predose
Safety Follow-up	(30 Days ± 7 Days after last dose)				

Abbreviations: ADA = antidrug antibody; EOI = end of infusion; PK = pharmacokinetic; Q3W = every 3 weeks.

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK and ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints.

Appendix 1C. Pharmacokinetic and Immunogenicity Sampling Schedule for BGB-A333 (Q2W)

	Cycle	Week	Day	PK Assessment	ADA Assessment
Treatment Period	1	1	1	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***6-hr (± 2 hr) (Phase 1 only)*** ***Day 2 (± 2 hr) (Phase 1 only)*** ***Day 4 (± 2 hr) (Phase 1 only)*** ***Day 8 (Phase 1 only)***	Predose
	2	3	15	Predose (-60 min to predose)	
	3	5	29	Predose (-60 min to predose) End of infusion (Within 30-min after EOI)	Predose
	7	13	85	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***Day 8 (Phase 1 only)***	Predose
	8	15	99	***Predose (-60 min to predose) (Phase 1 only)***	Predose
	13	25	169	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	19	37	253	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	25	49	337	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	37	73	505	Predose (-60 min to predose)	Predose
	37 +8.	73 +24.		Predose every 6 months after	Predose
Safety Follow-up	(30 Days ± 7 Days after last dose)				

Abbreviations: EOI = end of infusion; PK = pharmacokinetic; Q2W = every 2 weeks.

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK & ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints.

Appendix 1D. Pharmacokinetic and Immunogenicity Sampling Schedule for BGB-A333 (Q4W)

	Cycle	Week	Day	PK Assessment	ADA Assessment
Treatment Period	1	1	1	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***6-hr (± 2 hr) (Phase 1 only)*** ***Day 2 (± 2 hr) (Phase 1 only)*** ***Day 4 (± 2 hr) (Phase 1 only)*** ***Day 8 (Phase 1 only)*** ***Day 15 (Phase 1 only)*** ***Day 21 (Phase 1 only)***	Predose
	2	5	29	Predose (-60 min to predose) End of infusion (Within 30-min after EOI)	Predose
	4	13	85	Predose (-60 min to predose) End of infusion (Within 30-min after EOI) ***Day 8 (Phase 1 only)*** ***Day 15 (Phase 1 only)*** ***Day 21 (Phase 1 only)***	Predose
	5	17	113	Predose (-60 min to predose) End of infusion (Within 30-min after EOI)	Predose
	7	25	169	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	10	37	253	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	13	49	337	Predose (-60 min to predose) ***End of infusion (Within 30-min after EOI) (Phase 1 only)***	Predose
	19	73	505	Predose (-60 min to predose)	Predose
	25	97	673	Predose (-60 min to predose)	Predose
	25 +8.	97 +24.		Predose every 6 months after	Predose
Safety Follow-up	(30 Days ± 7 Days after last dose)				

Abbreviations: ADA = antidrug antibody; EOI = end of infusion; PK = pharmacokinetic; Q4W = every 4 weeks.

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK & ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints.

Appendix 1E. Pharmacokinetic and Immunogenicity Sampling for Tislelilzumab

	Cycle	Week	Day	PK Assessment	ADA Assessment
Treatment Period	1	1	1	Predose (-60 min to predose) End of infusion (End infusion to 30 min after EOI)	Predose
	2	4	22	Predose (-60 min to predose)	Predose
	5	13	85	Predose (-60 min to predose) End of infusion (End infusion to 30 min after EOI	Predose
	6	16	106	Predose (-60 min to predose)	
	9	25	169	Predose (-60 min to predose)	Predose
	13	37	253	Predose (-60 min to predose)	Predose
	17	49	337	Predose (-60 min to predose)	Predose
	25	73	505	Predose (-60 min to predose)	Predose
	33	97	673	Predose (-60 min to predose)	Predose
	33 +8.	97 +24.		Predose every 6 months after	Predose
Safety Follow-up	(30 Days ± 7 Days after last dose)				

Abbreviations: ADA = antidrug antibody; EOI = end of infusion; PK = pharmacokinetic.

Note: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK & ADA should be from a different site. Window: ± 30 minutes for EOI and ± 60 minutes for all other timepoints.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical Chemistry	Hematology	Coagulation[b]	Urinalysis
Alkaline phosphatase	RBC count	Prothrombin time	Glucose
Alanine aminotransferase	Hematocrit	Partial thromboplastin time	Protein
Aspartate aminotransferase	Hemoglobin	International normalized ratio	Blood
Albumin	Platelet counts		Ketones
Total bilirubin	WBC count with differential		24-hour protein[c]
Direct bilirubin	Neutrophil count		pH
Blood urea nitrogen or urea	Lymphocyte count		Specific gravity
Potassium	Monocyte count		
Sodium	Basophil count		
Calcium	Eosinophil count		
Creatinine			
Glucose			
Lactate dehydrogenase			
Total protein			
Testosterone[a]			
Creatine kinase			
Creatine kinase-cardiac muscle isoenzyme (CK-MB)[d]			

Abbreviations: aPTT = activated partial thromboplastin time; INR = International Normalized Ratio WBC = white blood cell.

a. Testosterone test is only applied for patients with mCRPC. However, the testosterone levels do not need to be checked if the patient has undergone surgical castration for > 4 months. Patients receiving chemical castration should have testosterone levels checked at baseline and confirmed to be in the castrate levels (< 0.5 ng/mL or 1.735 nM).
b. Coagulation tests are required at baseline and subsequently as clinically indicated (eg, patients with underlying coagulation disorder)
c. On routine urinalysis, if urine protein is ≥ 2+ by dipstick, then obtain a 24-hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio
d. If CK-MB fractionation is not available, troponin I and/or troponin T should be assessed instead.

In addition, the following tests will be conducted in this study:

- **Serum pregnancy test** (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to administration of study drug(s). **Urine or serum pregnancy tests** will be performed before study drug administration at each cycle and at Safety Follow-up. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal. A negative pregnancy test (by urine or serum) must be completed and recorded before administration of study drug(s) at each cycle
- **Thyroid function testing** (thyroid-stimulating hormone [TSH], free T3, free T4) will be performed at Screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc), and at the Safety Follow-up Visit (see Section 7.3.4 for details).

APPENDIX 3. ECOG PERFORMANCE STATUS

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

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

APPENDIX 4. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

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

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

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

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL", "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device
- Intrauterine hormone-releasing system
- 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 (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

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

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

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

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

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

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

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

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

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

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

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

The CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when eGFR values above 60 mL/min/1.73 m^2 are desired.

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1\ 209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

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

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

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

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

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

APPENDIX 8. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

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

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

- What was the temporal relationship between initiation of tislelizumab and the adverse event?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the irAE field associated with the AE in the eCRF should be checked.

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

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

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if Grade 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB (if CK-MB fractionation is not available, troponin I and/or troponin T should be assessed instead), and refer to a cardiologist.

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

Treatment of Immune-related Adverse Events

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone $\leq$ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening symptoms	If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.

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

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

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks	Hold study treatment until improved to grade 0-1
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to grade 0-1. Discontinue if any evidence of myocardial involvement
Myocarditis	**<2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2	Hold study treatment. If a diagnosis of myocarditis is confirmed, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study medical monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1g/day and add MMF, infliximab or anti-thymocyte globulin	
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

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

APPENDIX 9. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:
Eisenhauer EA, Therasse P, Bogaerts J, 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.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

Measurable Disease

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

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

Non-measurable Disease

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

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

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

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

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

Non-target Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological

confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 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, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly

coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Non-target Lesions

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

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more non-target 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 non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).

  Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing

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

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

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

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

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

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

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in 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 is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best

response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

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

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

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

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

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

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this

circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

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

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

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

APPENDIX 10. IRECIST CRITERIA

Table 1: Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	**iRECIST**
Definition of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ⩾10 mm in diameter (⩾ 15mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ⩾10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomized trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances-eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumors. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Source: Seymour L et al, 2017.

Table 2: Assignment of Timepoint Response Using iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

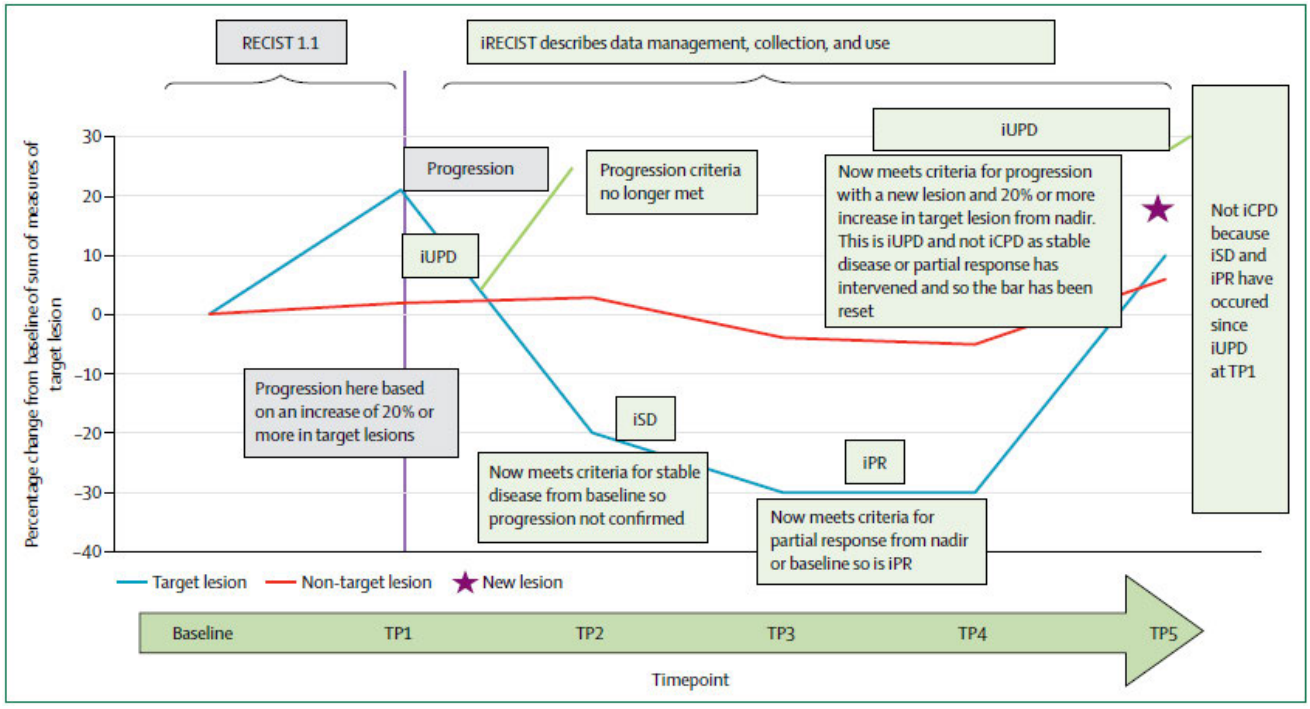
Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumors.
Source: Seymour L et al, 2017.

Table 3: Scenarios of Assignment of Best Overall Response Using iRECIST

	Timepoint response 1	**Timepoint response 2**	**Timepoint response 3**	**Timepoint response 4**	**Timepoint response 5**	**iBOR**
Example 1	iCR	iCR, iPR, iUPD, or NE	iCR, iPR, iUPD, or NE	iUPD	iCPD	iCR
Example 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Example 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Example 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, or NE	iPR
Example 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, or NE	iSD
Example 6	iUPD	iCPD	Any	Any	Any	iCPD
Example 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Example 8	iUPD	NE	NE	NE	NE	iUPD

Eight examples are presented for patients with target disease at baseline, but many more scenarios exist following the same principles. Table assumes a randomized study in which confirmation of complete response or partial response is not required. For patients with non-target disease only at baseline, only iCR or non-complete response or non-progression of disease can be assigned at each timepoint (not shown in the table for ease of presentation). "i" indicates immune responses assigned using iRECIST. iBOR=best overall response. iCR=complete response. iPR=partial response. NE=not evaluable. iUPD=unconfirmed progression. iCPD=confirmed progression. iSD=stable disease. RECIST=Response Evaluation Criteria in Solid Tumors.
Source: Seymour L et al, 2017.

Figure 1: RECIST 1.1 and iRECIST: an example of assessment



Prefix "i" indicates immune responses assigned using iRECIST; others without "i" are confirmed by RECIST 1.1.
RECIST=Response Evaluation Criteria in Solid Tumors.
iCR=complete response. iCPD=complete progression. iPR=partial response. iSD=stable disease.
iUPD=unconfirmed progression. TP=timepoint.
Source: Seymour L et al, 2017.

APPENDIX 11. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows:

Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637

Pugh RNH, Murray-Lyon IN, Dawson DL, Pietroni MC, and Williams R. Transection of the esophagus for bleeding esophageal varices. Brit J Surgery. 1973;60:646-645

Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481

Child-Pugh classification is either Grade A (mild: score 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: from 10 to 15 points) and is determined by both clinical and biochemical parameters (as shown below).

Clinical/Biochemical Parameter	**Score (Anomaly Severity)**		
	1	**2**	**3**
Hepatic encephalopathy (NCI-CTCAE grade)[a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites (presence and severity)	None	Mild	Moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prolonged prothrombin time (seconds) or Activated partial thromboplastin time (INR[g])	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

a. Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.

b. Grade 0: Consciousness, personality, neurological examination, and electrocardiogram are all normal.

c. Grade 1: Restlessness, sleep disorders, irritability/anxiety, hand tremor, writing disorders, 5CPS waves.

d. Grade 2: Lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.

e. Grade 3: Drowsiness, coma, orientation disorder, over-reflection, stiff/slow wave.

f. Grade 4: Cannot wake up from coma, no independent personality/behavior, irrational, slow 2-3CPS Delta activity.

g. Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg. 1997;3(6):628-637.

Abbreviations: INR, international normalized ratio; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.