CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma
Protocol Identifier:	BGB-A317-208
Phase:	2
Investigational Product:	Tislelizumab (BGB-A317)
Indication:	Previously Treated Unresectable Hepatocellular Carcinoma
Reference Number:	EudraCT 2017-003983-10
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1900 Powell Street, Suite 500 Emeryville, CA 94608 USA
Sponsor Medical Monitor:	[redacted] 1900 Powell Street, Suite 500 Emeryville, CA 94608 USA Phone number: [redacted] Email: [redacted] [redacted] China Phone number: [redacted] Email: [redacted]
Original Protocol:	13 September 2017
Amendment 1.0:	29 November 2017
Amendment 2.0:	25 June 2018

Confidentiality Statement

This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the sponsor.

FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma

BeiGene, Ltd. Approval:

[redacted] _____ 7/2/2018

Sponsor Medical Monitor — Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma

Protocol Identifier: BGB-A317-208

This protocol is a confidential communication of BeiGene, Ltd and its subsidiaries. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd or one of its subsidiaries.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 2.0 (25 JUNE 2018)

The primary purpose of this amendment is to incorporate feedback from the Food and Drug Administration (FDA) and the Health Authorities of Germany and France. Additions are in **bold text** and deletions are designated by ~~strike through text~~.

Section [a]	Key Change	Rationale for change
Title Page, Synopsis, Section 1.4	Introduced use of "Tislelizumab" as generic name of BGB-A317 by changing BGB-A317 to Tislelizumab (BGB-A317) on the title page, at first use in the synopsis (Investigational Product), and first use in the body of the amendment (Section 1.4)	To align with the current BeiGene protocol template
Synopsis	Updated the previously approximated number of participating study centers from "45" centers internationally to "80"	To address increase in global site selection to meet enrollment target need
	Sponsor Medical Monitor contact information updated: [redacted]	Change in Medical Monitor
Synopsis Section 4.1	Added "**or acceptable age according to local regulations**" to age requirement in-text of the synopsis and to inclusion criteria #2	To accommodate country-specific regulations
Synopsis Section 9.1.1	Revised text: Efficacy Evaluable Population (EFF) includes all patients in the SAF with measurable disease at baseline per RECIST 1.1 who had at least one evaluable post-baseline tumor assessment unless discontinued due to clinical disease progression or death within ~~10 weeks~~ **7 weeks** of the first dose date.	To align with current imaging schedule (6 weeks ±7 days during the first 18 weeks)
Synopsis Section 9.2.1	Added text: **In case of significant enrollment delay in the second line or third line (or more) population, a sub-population focused analysis may be performed once a given population has reached its enrollment target.**	To allow the possibility of focused analyses if deemed necessary and appropriate.
Synopsis Section 9.3.2	Added text: Treatment-emergent AEs also include **all** irAEs **and related serious** AEs recorded up to 90 days after the last dose of BGB-A317 regardless of whether or not the patient starts a new anticancer therapy.	Clarification text
Synopsis Section 9.7	Revised sample size considerations by adding text: **Within 2nd line or 3rd line plus patients, the 95% CI of the same ORR is (8.6%, 23.5%) when n=100 in each population**.	To provide additional statistical information for clarification as per agreement with FDA feedback
Section 3.3.4	Provided clarification to Survival Follow-up Period by adding text: **Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor, whichever occurs first.**	To align with current BeiGene Protocol template
Section 4.1	Revised text to Inclusion Criteria #6: Patients receiving antivirals at Screening should have been treated for > 2 weeks prior to enrollment and should continue treatment ~~on study~~**for 6 months after study drug treatment discontinues**.	Updated to incorporate FDA's request to implement measures to further decrease the potential for viral reactivation

Section [a]	Key Change	Rationale for change
Section 4.1	Revised text in inclusion criteria 7a: Absolute neutrophil count (ANC) ≥ 1500/mcl, platelets ≥ 60000/mcl, hemoglobin ≥ 85 g/L or ~~5.6~~**5.3** mmol/L	Correction of conversion from g/L to mmol/L
Section 4.1	Clarification to inclusion criteria 7b: Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/**1.73m²** by Chronic Kidney Disease Epidemiology Collaboration equation.	To correct inconsistency with Appendix 9 Chronic Kidney Disease Epidemiology (CKD-EPI) Equation and incorporate German Health Authority feedback
Section 8.7.4	Added text: Patients with moderate renal dysfunction (estimated glomerular filtration rate > 30 mL/min/**1.73m²** and < 60mL/min/**1.73m²** by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study.	
Section 5.2	Revised text: BGB-A317 will be administered by IV infusion, **preferably** using a volumetric pump through an IV line containing a sterile, non-pyrogenic, low-protein-binding filter.	Use of a volumetric pump is recommended, however, alternative methods in accordance with institutional procedures are also permitted
Section 5.3	Added clarification text: Any overdose (**defined as ≥ 600 mg of BGB-A317 in a 24-hour period**) or incorrect administration of study drug should be noted on the study drug administration electronic case report form (eCRF).	To provide clarification to reporting of study treatment overdose and align with definition for overdose of study treatment in current BeiGene protocol template
	Revised text: ~~If~~ **Any SAEs associated with** an overdose or incorrect administration ~~of study treatment takes place, the sponsor is~~**are** required to be ~~immediately notified~~ **reported within 24 hours of awareness via SAE reporting process as described in Section 8.7. Supportive care measures should be administered as appropriate**.	
Section 6.1.1	Provided clarification text: Patients with active hepatitis B defined as either detectable HBsAg or HBV DNA at baseline must **initiate treatment 2 weeks prior to first dose and continue until 6 months after the last dose. Patients should** ~~or~~ continue effective antiviral treatment during the study to decrease potential viral re-activation risk.	Updated to incorporate FDA's request to implement measures to further decrease the potential for viral reactivation
	Revised text: Management of antiviral therapy is at the discretion of the investigator; **however, reason(s) must be provided in the CRF if a patient with active hepatitis B is not treated with antiviral prophylaxis.** **BeiGene does not require patients** with active hepatitis C ~~may undergo~~ to receive treatment with antiviral therapy. **Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals** following the AASLD guideline (https://www hcvguidelines.org) 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 first dose.**	Revised HBV/HCV language to align per other BeiGene protocols and to incorporate FDA's request to implement measures to further decrease the potential for viral reactivation

Section [a]	Key Change	Rationale for change
Section 6.1.1	Added text: **Palliative (limited-field) radiation therapy should not have been administered within 4 weeks before enrollment.**	Clarification text to indicate that 4-week washout period should also be observed for prior palliative radiation therapy
	Added text: The case is discussed with sponsor medical monitor **to ensure study compliance,** and sponsor medical monitor agrees that the conditions required to receive palliative radiation are met	Clarification text to address German Authority feedback and to clarify the responsibility of the medical monitor on study
Section 6.1.2	Revised text: Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat ~~or control~~ a treatment-emergent drug-related AE or for short-term use as prophylactic treatment.	Clarification to prohibited or restricted concomitant medication guidelines for consistency with Appendix 7, where control of irAEs is defined and to align with current BeiGene protocol template
	Added text: **However, Opiates and other medications required for palliative management of patients are allowed**.	
Section 7.1	Added text: **Patients who have within 6 months before first study drug administration any clinical evidence of portal hypertension with bleeding esophageal or gastric varices, or those that have undergone any major surgical procedure within 28 days before first study drug administration, should be considered to have a serious underlying medical condition that would be unfavorable for the administration of study drug**.	To provide clarity to patient screening regarding serious medical conditions that would be considered unfavorable for the administration of study drug, in accordance with exclusion criterion #18
Section 7.1.1	Added text: Cancer history will include an assessment of prior surgery, prior radiotherapy**, prior loco-regional therapy,** prior drug therapy, including start and stop dates, best response and reason for discontinuation.	Clarification to cancer history assessment
Section 7.1.2.2	Added text: **Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide**	Update to contraception guidelines per the EU Clinical Trial Facilitation Group (CTFG)
	Added text: **Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success**	
	Added definition of a sterile male: **A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility**	
	Revised text: 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 used in combination with **one of the highly effective forms of birth control** ~~another acceptable method~~ listed above	
Section 7.1.5 Appendix 1	Removed New York Heart Association (NYHA) Functional Classification from schedule of assessments as it is only intended for assessment of the severity of heart failure which is an exclusion criterion.	Clarification to schedule of assessments as NYHA is only intended for assessment of severity of heart failure prior to enrollment

Section [a]	Key Change	Rationale for change
Section 7.4.4	Revised text: If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed ~~before study drug administration~~ **prior to treatment authorization**.	Clarification to laboratory safety test sample collection to ensure that required screening lab results within 7 days of first study dose are available and reviewed prior to treatment authorization and to align with current BeiGene protocol template and that safety lab results after cycle 1 are available and reviewed within 2 days of each subsequent dose
Section 7.5	Added text: **Patients must have at least one (1) measurable lesion according to RECIST v1.1 at baseline, provided that:** • **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**	Clarification regarding the determination of measurable disease at baseline in the context of prior locoregional therapies
	Added text: **MRI may be used when it is the standard of care at a site, regardless of whether or not CT is contraindicated.**	Clarification to allow MRI scans to be used if they are local standard of care
	Added instruction for collection of tri-phasic scans as follows: **The liver should be imaged using tri-phasic scans (ie, late arterial phase, portal venous phase and delayed/equilibrium phase are required). Every effort should be made to keep the methodology consistent across visits for a subject (ie, phases acquired, timing for each phase, etc). Scanning details will be provided by the imaging vendor in a separate site manual.**	Clarification to require the collection of tri-phasic scans when possible, which is standard of care in HCC. This will facilitate adequate disease assessments in this setting and comparison to historical studies
Section 7.10	Revised detail for physical examination: Unscheduled visits may be performed at any time at the patient's or investigator's request and may include vital signs/focused physical examination; ECOG performance status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination ~~of liver, spleen, and lymph nodes; disease-related constitutional symptoms~~; and hematology and chemistry laboratory assessments.	Clarification to ensure comprehensive physical exam assessments are performed
Section 7.13.2	Added text: **Patients who, in the opinion of the Investigator, continue to benefit from tislelizumab at study termination, will be offered the option to continue treatment in a company-sponsored clinical trial until it is commercially available in the country.**	Clarification per French Health Authority feedback and to align with current BeiGene protocol template
Section 8.2.1	Revised text: Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, **patients who have undergone allogenic stem cell or organ transplantation,** and patients who have received a live viral vaccine within 28 days before study drug administration, are excluded from the study (see Section 4.2 for the full list of exclusion criteria).	For alignment with inclusion/exclusion criteria

Section [a]	Key Change	Rationale for change
Section 9.1.3	Revised text: Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include, gender, ECOG, geographical region, country, race, Child-Pugh classification, hepatitis virus, BCLC staging, ~~TNM staging,~~ metastatic site, and macrovascular invasion and/or extrahepatic spread status.	Not using TNM staging in this protocol
Section 13.5	Revised text: This is intended to ensure financial interests and arrangements of the clinical investigators with **parties supporting the study**~~BeiGene (and affiliates)~~ that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor.	To ensure coverage of BeiGene's affiliates
Section 14.1.1	Revised text: The investigator or **delegated** designee, **who is included** on Form FDA 1572 **(or equivalent, such as a Statement of Investigator, as applicable for Non-US Investigators)**, must sign the completed casebooks to attest to its accuracy, authenticity, and completeness	Clarification text
Appendix I	Added 2- or 3-day windows to assessment days Cycles 1 to 3 of the treatment period	To provide reasonable opportunity to complete assessments
	Added text to footnote #11: **If the screening urine pregnancy test has not been done within 7 days of first dose, it would need to be repeated at Cycle 1 Day 1, prior to dosing.**	Clarification text to address German Authority feedback
	Added text to footnote #15: **Results of pulmonary function testing should be reviewed prior to treatment authorization.**	Clarification text
	Revised footnote #16: Testing will be performed by the local/central laboratory at screening and include ~~HIV testing and~~ HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).	HIV testing is not required for eligibility; protocol clarification memo was incorporated into this amendment
	Added footnote #26: **All Child-Pugh classification (Appendix 2) evaluations must be performed within 7 days of first study drug administration**.	To align with inclusion criteria 3c to ensure that all Child Pugh related evaluations are contemporaneous with patient enrollment and to provide clarification to timing
	Added Quality of Life (QOL) questionnaires, (EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-HCC18) to End of Treatment assessments	To provide clarification to the timing of these QOL assessments
Appendix 4	Added assessment: **Creatine kinase** **Creatine kinase-cardiac muscle isoenzyme (CK MB)[2]**	Additional assessments are being implemented to monitor for myocarditis/myositis during the study
	Added footnote #2: **In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.**	
Appendix 7	Revised guidelines for treatment of immune-related adverse events throughout appendix	To provide consistency with current BeiGene protocol template and to provide clarification to protocol irAE evaluation and management guidelines

Section [a]	Key Change	Rationale for change
Appendix 7	Clarification to immune-related toxicity eye disorders: If patients experience **acute, new onset, or worsening** eye inflammation, blurred vision or other visual disturbance refer the patient urgently to an ophthalmologist for evaluation and management.	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to immune-related toxicity as follows: ~~Rheumatology~~**Joint or muscle inflammation** and added text: **For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy**.	To provide clarification to protocol irAE evaluation and management guidelines
	Added immune-related toxicity: Myocarditis: Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.	To provide clarification to protocol irAE evaluation and management guidelines
	Update to thyroid disorder treatment guidelines as follows: Grade 3-4: Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.~~5~~6 µg/kg/day. (for the elderly or those with co morbidities, the suggested starting dose is 0.5 µg/kg/day).	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to definition of hypophysitis: Grade 1-2: Mild-moderate symptoms Grade 3-4: ~~Moderate-severe~~Severe or life-threatening symptoms	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to pneumonitis treatment guideline: Grade 3-4 ~~Initiate~~**Admit to a hospital and initiate** treatment with IV methylprednisolone 2 4 mg/kg/day.	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to neurological toxicity treatment guideline: Grade 2: Taper over at least ~~1 month~~**4 weeks. Obtain neurology consultation.** Grade 3-4: Taper corticosteroids over at least ~~1 month~~**4 weeks**. Consider azathioprine, MMF, cyclosporine if no response **within 72-96 hours**.	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to colitis/diarrhea treatment guideline: Grade 2: Taper steroids over 2 4 weeks~~.~~, **consider endoscopy if symptoms are recurring;** Hold study treatment; resume when resolved/improved to **baseline** grade ~~0~~ 1. Grade 3: Convert to oral prednisolone and taper over at least ~~1 month~~**4 weeks**; Hold study treatment; retreatment may be considered when resolved/improved to **baseline** grade ~~0~~ 1 and after discussion with the study medical monitor	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to skin reactions treatment guideline: Grade 2: **Consider a short course of oral steroids.** Grade 3: For severe symptoms: IV methylprednisolone 0.5 1 mg/kg/day; convert to oral prednisolone and taper over ~~2~~ **at least** 4 weeks. Grade 4: ~~Seek~~**Admit to a hospital and seek** urgent dermatology review.	To provide clarification to protocol irAE evaluation and management guidelines

Section [a]	Key Change	Rationale for change
Appendix 7	Revision to hepatitis treatment guideline: Grade 1: 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.** Grade 2: Hold study treatment, treatment may be resumed when resolved/improved to **baseline** grade ~~0-1~~ and prednisolone tapered to ≤ 10 mg. Grade 3: When LFTs improve to grade 2 or lower, convert to oral prednisolone and taper over at least ~~1 month~~**4 weeks**; Hold study treatment until improved to **baseline** grade ~~2~~	To provide clarification to protocol irAE evaluation and management guidelines
	Revision to nephritis treatment guideline Grade 2: If attributed to study drug and resolved/improved to **baseline** grade ~~0-1~~ Grade 3: Taper corticosteroids over at least ~~1 month~~**4 weeks**.	To provide clarification to protocol irAE evaluation and management guidelines
	Added autoimmune toxicity: **Myositis/ Rhabdomyolysis**: Grade **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.** Grade **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** Grade **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**	To provide clarification to protocol irAE evaluation and management guidelines

Section [a]	Key Change	Rationale for change
Appendix 7	Added autoimmune toxicity: **Myocarditis:** Grade **< 2: 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.** Grade **2: Symptoms on mild-moderate exertion,** Grade **3: Severe symptoms with mild exertion, and** Grade **4: Life-threatening: 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** **Study management** for Grades < 2, 2, 3, and 4**: 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**	To provide clarification to protocol irAE evaluation and management guidelines
Appendix 11	Added new appendix for Barcelona Clinic Liver Cancer (BCLC) staging classification	To provide additional guidance to screening procedures

[a] Refers to section number in Amendment 2.0 protocol.

TABLE OF CONTENTS

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SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.
Investigational Product: Tislelizumab (BGB-A317)
Title of Study: A Phase 2, Open-label, Multicenter Study to Investigate the Efficacy, Safety, and Pharmacokinetics of the Anti-PD-1 Monoclonal Antibody BGB-A317 in Patients with Previously Treated Hepatocellular Unresectable Carcinoma
Protocol Identifier: BGB-A317-208
Phase of Development: 2
Number of Patients: Approximately 228
Study Centers: Approximately 80 centers internationally
Study Objectives: **Primary:** • To evaluate the efficacy of BGB-A317 through Independent Review Committee (IRC) assessed objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 in previously treated, unresectable hepatocellular carcinoma (HCC) **Secondary:** • To assess the efficacy of BGB-A317 through duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), and clinical benefit rate (CBR) assessed by IRC and overall survival (OS) • To assess efficacy of BGB-A317 through ORR, DOR, PFS, DCR, and CBR assessed by the investigators • To assess the safety and tolerability of BGB-A317 in patients with previously treated unresectable HCC • To assess the health-related quality of life (HRQoL) of BGB-A317 in patients with previously treated unresectable HCC **Exploratory:** • To assess potential predictive biomarkers • To characterize the pharmacokinetics (PK) of BGB-A317 • To assess host immunogenicity to BGB-A317
Study Endpoints: **Primary:** ORR (complete response [CR] + partial response [PR]) based on RECIST v 1.1 in patients with previously treated unresectable HCC as evaluated by an IRC

Secondary:

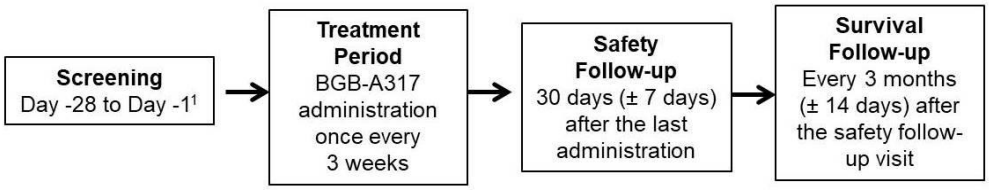
- DOR, PFS, DCR and CBR assessed by IRC, and OS
- ORR, DOR, PFS, DCR and CBR assessed by Investigators
- Safety and tolerability assessment of adverse events (AEs), serious adverse events (SAEs), physical examination, vital signs, electrocardiogram (ECG), and laboratory measurements
- HRQoL measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ HCC18) index score, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) index-score, and the 5-level version of the European Quality of Life 5-Dimensional Questionnaire (EQ-5D-5L)

Exploratory:

- Predictive biomarker (for example, programmed cell death protein ligand-1 [PD-L1] expression and gene expression in tumor tissue)
- PK: Summary of plasma concentrations of BGB-A317
- Immunogenicity: Assessments of immunogenicity of BGB-A317 to determine the incidence of anti-drug antibodies (ADAs)

Study Design:

This is a Phase 2, multicenter, open-label study in adults with previously treated unresectable HCC. Approximately 228 patients will receive BGB-A317 200 mg intravenously (IV) every 3 weeks (Q3W). The study design schema is as follows:



[1] Screening assessments will be completed within 28 days prior to the first dose of the study drug. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed before study drug administration.

After completing all Screening activities, patients confirmed by the sponsor to be eligible will receive open-label treatment with BGB-A317 until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy, whichever should occur first. Treatment beyond initial disease progression (as assessed by the investigator per RECIST v1.1) is permitted, provided that the patient meets protocol-specified criteria. Of the 228 patients, at least 100 patients will be enrolled who have had no more than 1 line of prior systemic therapy and at least 100 patients will be enrolled who have had at least 2 lines of prior systemic therapy.

Study Assessments:

Radiological assessment of tumor-response status should be performed every 6 weeks in the first 18 weeks then every 9 weeks thereafter. Tumor response will be assessed by an IRC and by investigators. Patients who discontinue study drug for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments until disease progression, withdrawal of consent, death, or start of a new

anticancer therapy, whichever occurs first.

Patients will be evaluated for any AEs occurring up to 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first (all severity grades, per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 4.03) and all immune-related adverse events (irAEs) occurring up to 90 days after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation.

Duration of Patient Participation:

Total duration of study participation will vary by patient.

Study Population:

Key Eligibility Criteria:

The population under study is adult patients (≥18 years of age on the day the patient voluntarily agrees to participate in the study or acceptable age according to local regulations) with histologically confirmed HCC that is classified as Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease that is not amenable to or has relapsed after locoregional therapy, and is not amenable to a curative treatment approach, and has received at least 1 line of systemic therapy for unresectable HCC (must have progressed on or is intolerant to, in the first-line setting, either sorafenib, chemotherapy, or an experimental therapy that has demonstrated efficacy in a Phase 3 study [eg, lenvatinib]). Patients may not have participated in a prior BeiGene clinical trial for the treatment of HCC. All patients are also required to be Child-Pugh Class A, have ≥ 1 measurable lesion per RECIST v1.1, and have an Eastern Cooperative Oncology Group Performance Status score of ≤ 1. Archival tumor tissues (if available) will be required for biomarker analysis at a central laboratory.

Test Product, Dose, and Mode of Administration:

BGB-A317 will be administered at a dose of 200 mg IV Q3W.

Reference Therapy, Dose, and Mode of Administration:

Not applicable.

Statistical Methods:

Populations:

The Safety Population (SAF) includes all patients who have received any dose of BGB-A317. It will be the primary population for efficacy and safety analysis.

The Efficacy Evaluable Population (EFF) includes all subjects in the SAF with measurable disease at baseline per RECIST 1.1 who had at least one evaluable post-baseline tumor assessment unless discontinued due to clinical disease progression or death within 7 weeks of the first dose date.

The PK population (PK) includes subjects who contributed at least 1 post-dose quantifiable PK sample.

Primary Efficacy Analyses:

Hypothesis testing of ORR per IRC in the SAF will be the primary efficacy analysis. Efficacy endpoints based on investigator-assessed tumor response will be presented as the secondary efficacy analyses.

The ORR of BGB-A317 per IRC is assumed as 15% in patients with previously treated unresectable HCC. The historical rate in a similar population is estimated as 7% (Bruix et al, 2017). The null and alternative hypotheses are set as follows:

H0: ORR = 7%

Ha: ORR ≥ 15%

A binomial exact test will be performed for hypothesis testing. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that BGB-A317 monotherapy statistically significantly increases ORR compared with historical control. Therefore, the superiority of BGB-A317 monotherapy will be demonstrated. A two-sided binomial exact 95% confidence interval (CI) of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, anticipated as no more than 6 months after the last subject received the first dose of study drug. In case of significant enrollment delay in the second line or third line (or more) population, a sub-population focused analysis may be performed once a given population has reached its enrollment target.

Secondary Efficacy Analyses:

Other tumor assessment outcomes per IRC or investigator will be summarized as well as OS as secondary efficacy analysis.

The Kaplan-Meier (KM) method will be used to estimate the key secondary endpoint DOR and corresponding quantiles (including the median), if estimable, in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982).

The DOR censoring rule will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007). Censoring rules following the European Medicines Agency Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA, 2012) will be used as a sensitivity analysis.

Other time to event variables (PFS and OS) will be similarly analyzed in the SAF using the KM method as described above. The KM estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis set who remain alive and progression-free at the specified time points (ie, 3 or 6 month), will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926). The OS time point estimates will be calculated similarly.

Binomial exact 95% CI of DCR and CBR will be calculated in the SAF.

Safety Analyses:

BGB-A317 exposure will be summarized by number of cycles received, duration, dosage, and dose intensity.

Verbatim AE terms will be mapped to the corresponding Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms and graded per NCI-CTCAE v4.03. All treatment-emergent adverse events (TEAEs) will be summarized. A TEAE is defined in this protocol as any AE with either an onset date or a date of worsening in severity from baseline (ie, pretreatment) occurring on or after first dose of study drug and up to either 30 days following discontinuation from study drug or start of new anticancer therapy. The TEAE classification also applies to all irAEs (BGB-A317 only) and related serious AEs that are recorded up to 90 days after discontinuation from BGB-A317, regardless of whether or not the patient starts a new anticancer therapy.

Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings. All SAEs, deaths, TEAEs of ≥ Grade 3

severity, TEAEs assessed by the investigator as treatment related, irAEs, and TEAEs leading to treatment discontinuation, dose interruption, or dose delay will be summarized. In all AE summary tables, multiple occurrences of the same AE will be counted once at the maximum severity grade within a particular MedDRA system organ class and preferred term.

All clinical laboratory and vital sign assessments with values outside the normal ranges will be identified.

Exploratory Analyses:

The primary predictive biomarker analysis is based on a subset of the patients with both a valid PD-L1 expression and/or tumor-infiltrating lymphocytes (TILs) measurement and at least one disease assessment post-treatment. A supportive analysis is based on patients with a valid PD-L1 expression and/or TILs measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response. Exploratory analyses of other candidate predictive biomarkers, including but not limited to gene expression profiling, will be conducted similarly.

Sample Size Considerations:

The ORR per IRC is assumed as 15% in this trial. With 228 patients, the power is 0.97 to demonstrate the ORR in patients with previously treated unresectable HCC is statistically higher than the historical rate of 7% in a binomial exact test. The 95% CI of an observed 15% ORR is (10.6%, 20.3%) when approximately 228 previously treated unresectable HCC patients are enrolled. Within 2nd line or 3rd line plus patients, the 95% CI of the same ORR is (8.6%, 23.5%) when n=100 in each population.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AASLD	American Association for the Study of Liver Disease
ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration time curve
BCLC	Barcelona Clinic Liver Cancer
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{trough}	trough serum concentration data
CP	Child-Pugh
CPS	cycles per second
CR	complete response
CSR	clinical study report
CT	computed tomography
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture (system)
EFF	Efficacy Evaluable Population
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-5L	5-level version of European Quality of Life 5-Dimensional Questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-HCC18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions
ESMO	European Society for Medical Oncology
Fc	fragment crystallizable region (typically, of immunoglobulin G)
FcγR	gamma Fc receptor (eg, Fcγ-RI, Fcγ-RIII)
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice

Abbreviation	Definition
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IFN-α	Interferon-alpha
IgG	immunoglobulin G (eg, IgG1, IgG2, IgG3, IgG4); other types of immunoglobulins include IgD and IgM
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
IV	intravenous(ly)
KM	Kaplan-Meier
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PD-L2	programmed cell death protein ligand-2
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance status
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SAF	Safety Population

Abbreviation	Definition
SD	stable disease
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	half-life
TACE	transarterial chemoembolization
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocytes
ULN	upper limit of normal
v	version

1. INTRODUCTION

1.1. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a major global health problem, accounting for 85-90% of all reported cases of liver cancer (a term with which HCC is often used interchangeably) (El-Seragl, 2012). According to the World Health Organization's GLOBOCAN 2012 database, liver cancer was the sixth most common type of cancer that year, with 782,000 new cases worldwide; it was also the second most common cause of cancer-related mortality, responsible for an estimated 746,000 deaths (Torre et al, 2015).

Most HCC cases (> 80%) occur in Eastern Asia and in sub-Saharan Africa, with typical incidence rates of > 20 per 100,000 individuals. China alone accounts for approximately 50% of both new HCC cases and HCC-related deaths worldwide (Torre et al, 2015). Southern European countries, such as Spain, Italy, and Greece, tend to have more moderate incidence rates (~10 to 20 per 100,000 individuals), whereas North America, South America, Northern Europe, and Oceania have a relatively low incidence of HCC (< 5 per 100,000 individuals; El-Serag, 2012).

A variety of risk factors are known to be causative for HCC. These include infection with hepatitis viruses, aflatoxin B, tobacco, vinyl chloride, heavy alcohol intake, non-alcoholic fatty liver disease, hemochromatosis, and diabetes. Together, hepatitis B virus (HBV) and hepatitis C virus (HCV) account for 80-90% of all HCC cases worldwide (Bosch et al, 2005). Chronic HBV infection is the dominant risk factor for the disease in most areas of Asia, with the exception of Japan (El-Serag, 2012), while chronic infection with HCV is the leading cause of HCC in Western countries and in Japan (Choo et al, 2016).

Treatment options for HCC are based on the stage of the disease at diagnosis per the Barcelona Clinic Liver Cancer (BCLC) classification system, which draws from a combination of Eastern Cooperative Oncology Group (ECOG) Performance Status (PS; Appendix 3), Child-Pugh (CP) classification criteria for liver function (Appendix 2), and extent of disease (Llovet et al, 2004) to define disease staging for HCC. Approximately 30% of HCC cases are diagnosed at the early stages (ie, BCLC stages 0 or A) and are amenable to potentially curative treatments, including liver transplantation, resection, or locoregional procedures such as radiofrequency ablation and percutaneous ethanol injection. However, there is a high rate (70%) of HCC recurrence within 5 years (Oikonomopoulos et al, 2016).

In intermediate-stage HCC (ie, BCLC Stage B), transarterial chemoembolization (TACE) is the recommended treatment modality (Han et al, 2015) for these patients, but the data are difficult to interpret in the context of BCLC staging; the data supporting the recommendation were not categorized according to BCLC classification (Han et al, 2015). Nonetheless, patients do progress after TACE treatment and become ineligible for further TACE therapy.

For patients with advanced disease (ie, BCLC Stage C), sorafenib, a multitargeted tyrosine kinase inhibitor, is the only globally approved systemic therapy for first-line HCC (Keating et al, 2017). Regorafenib was recently approved in key global regions for the treatment of second-line HCC including the United States (US), the European Union, and Japan.

1.2. Current Treatment of Hepatocellular Carcinoma

The majority (approximately 70%) of patients diagnosed with HCC present with unresectable disease (Mazzaferro et al, 1996). In 2008, sorafenib, a multi-kinase inhibitor, was approved by the US Food and Drug Administration (FDA) for use in this patient population. It inhibits multiple intracellular (CRAF, BRAF) and cell surface kinases (KIT, FLT-3, RET, VEGFR1/2/3, and PDGFRβ), which impede tumor growth and angiogenesis. The clinical efficacy of sorafenib in the HCC patient population has been well-documented in 2 key studies (Balogh et al, 2016). Chemotherapy has also been used in the treatment of HCC in certain regions globally. The EACH study demonstrated a superior overall survival (OS) for a FOLFOX4 regimen (oxaliplatin, 5-fluorouracil, and leucovorin) compared with doxorubicin alone in patients with advanced HCC with a median OS of 6.47 months (95% confidence interval [CI], 5.33-7.03) in the study arm (Qin et al, 2013).

Patients with unresectable previously treated HCC represent a population with a great unmet medical need. Overall survival in this patient population is limited, typically 6 months or less. Beyond sorafenib or chemotherapy, however, there is no recognized treatment standard. Recently published in December 2016, a global study of regorafenib in advanced HCC (RESORCE trial, Bruix et al, 2017) showed an improved median OS in patients with disease progression following sorafenib treatment, which was 10.6 months (95% CI, 9.1-12.1) compared with placebo (7.8 months, 95% CI, 6.3-8.8). Given the poor patient outcomes of standard of care treatments, clinical trials are often given as alternative treatment. Investigational agents include but are not limited to lenvatinib in the first line setting, where it demonstrated non-inferior OS compared to sorafenib (Cheng et al, 2017) and cabozantinib in the second-line setting, where a positive study outcome was recently announced by the company (Ipsen Press Release, 2017). Regardless, survival remains poor, and additional therapeutic options are therefore required for the second-line setting and beyond.

1.3. Anti-PD-1/Anti-PD-L1 Therapy for Advanced Hepatocellular Carcinoma

The immune checkpoint-inhibitory receptor known as programmed cell death protein-1 (PD-1) is mainly expressed in activated T-cells (Topalian et al, 2012; Bersanelli et al, 2017). The PD-1 signaling cascade negatively regulates T-cell receptor activities while attenuating T-cell proliferation and function, with the ultimate consequence of T-cell exhaustion.

The expression of PD-1 is markedly upregulated in tumor-infiltrating lymphocytes, and the expression of programmed cell death protein ligand-1 (PD-L1) is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines (eg, interferon-alpha [IFN-α] and interferon gamma [IFN-γ]) in the tumor microenvironment. Furthermore, increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor cells and tumor-associated stromal cells have been observed in many types of solid tumors (Jin et al, 2016; Ono et al, 2017; Patel et al, 2015; Van Der Kraak et al, 2016; McDaniel et al, 2016; Gong et al, 2011).

These data provide a basis for the use of PD-1 antagonists as immuno-oncologic agents. The therapeutic approach of blocking PD-1 and PD-L1 interactions has recently demonstrated efficacy in a variety of tumor types. Monoclonal antibodies to PD-1, such as nivolumab and pembrolizumab, have the ability to bind to PD-1, thus disrupting interactions between the protein and its ligands (PD-L1 and programmed cell death

protein ligand-2 [PD-L2]) and impeding inhibitory signals in the T-cell microenvironment (Wang et al, 2014). These monoclonal antibodies have now been approved for the treatment of several cancers, including bladder, lung, head and neck squamous cell carcinomas, as well as melanoma, in the US, Europe, and beyond.

Recently published results from an ongoing, open-label, Phase 1b/2 study of nivolumab in patients with advanced HCC ("CheckMate040"; El-Khoueiry et al, 2017) include an objective response rate (ORR) of 20% (95% CI: 15-26) in 214 patients treated in the study's dose expansion phase. The median duration of response (DOR) for all patients in the dose-escalation phase was 9.9 months and the 9-month OS rate was 74% (95% CI: 67-79%). These results are very promising and suggest the potential efficacy of anti-PD-1 antibodies as therapies for patients with advanced-stage, or otherwise difficult-to-treat, HCC. The US FDA recently granted accelerated approval of nivolumab for the treatment of HCC previously treated with sorafenib (FDA Press Release, 2017).

1.4. Background Information on Tislelizumab (BGB-A317)

1.4.1. Pharmacology

Tislelizumab (BGB-A317) is a humanized, immunoglobulin G4 (IgG)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

BGB-A317 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 PD-L2, thus inhibiting PD-1-mediated negative signaling in T-cells. In *in vitro* cell-based assays, BGB-A317 was observed to consistently and dose-dependently enhance the functional activity of human T-cells and pre-activated, primary peripheral blood mononuclear cells. In addition, BGB-A317 has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cell were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

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

Please refer to the BGB-A317 Investigator's Brochure for additional details regarding nonclinical studies of BGB-A317.

1.4.2. Toxicology

The toxicity and safety profile of BGB-A317 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 Good Laboratory Practice regulations. The single dosing regimens were spanning from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat dosing regimens spanning

to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies at a single dose up to 100 mg/kg. 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 proportionally 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 of BGB-A317 in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of BGB-A317 is considered adequate to support first-in-human dose safely and ethically.

Please refer to the BGB-A317 Investigator's Brochure for more detailed information on the toxicology of BGB-A317.

1.4.3. Clinical Pharmacology

An interim pharmacokinetic (PK) analysis (data cutoff date of 08 October 2016) was conducted by noncompartmental analysis methods, using serum concentrations from patients who received doses of BGB-A317 0.5, 2.0, 5.0, and 10 mg/kg every 2 weeks (Q2W) and patients who received doses of 2.0 and 5.0 mg/kg every 3 weeks (Q3W) in BGB-A317_Study_001 (Phase 1a, part 1 and part 2). The maximum observed plasma concentration (C_{max}) and drug exposure (ie, the area under the concentration-time curve [AUC]) increased in a nearly dose-proportional manner from 0.5 mg/kg to 10 mg/kg, both after single-dose administration and at steady-state.

Population PK analysis was conducted with a 2-compartment model with first order elimination. Systemic clearance of BGB-A317 was 0.00794 L/h, volume of distribution in the central and peripheral compartment were 2.75 and 1.65 L, respectively, and terminal elimination half-life ($T_{1/2}$) was approximately 17 days.

Patients' body weight is not a significant covariate on the clearance of BGB-A317, a finding that supports fixed dosing of BGB-A317.

1.4.3.1. Lack of Ethnic Differences in Exposure

Based on the information available to date, BGB-A317 exposure in Asian and Caucasian patients is similar, and the safety profile at clinically relevant doses is tolerable and manageable.

Preliminary PK data from BGB-A317_Study_001 are summarized in Section 1.4.3 above. Comparison of PK parameters indicates that after a single IV infusion of BGB-A317, dose normalized exposure was consistent across Asian (n=10) and Caucasian (n=93) patients in the study, which was conducted in the US, Australia, New Zealand, Korea, and Taiwan. Additionally, dose-normalized exposure was consistent between BGB-A317_Study_001, in which most patients were Caucasian (n=107) and Study BGB-A317-102, conducted in Chinese patients (n=6).

These preliminary findings indicate that ethnic differences are unlikely to affect the exposure of BGB-A317.

Furthermore, these data are consistent with findings of limited ethnic differences in studies of therapeutic monoclonal antibodies (Chiba et al, 2014). In addition, there do not appear to be clinically relevant differences in PK exposures from studies of 2 other anti-PD-1 antibodies, nivolumab and pembrolizumab.

1.4.4. Prior Clinical Experience of BGB-A317

There are 6 currently ongoing studies with BGB-A317 in patients with various solid tumor types. Preliminary data is only available from BGB-A317_Study _001, which are summarized below.

Refer to the Investigator's Brochure for more detailed information on the clinical experience of BGB-A317.

1.4.4.1. BGB-A317_Study_001 Phase 1a

As of 13 January 2017, 111 patients with solid tumors have been treated with BGB-A317 in BGB-A317_Study_001 for parts 1, 2, and 3 combined. Patients had received BGB-A317 treatment in Phase 1a 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. The median duration of treatment for the combined subject population was 85 days (range: 1 to 471 days). A maximum tolerated dose (MTD) has not been determined. The recommend Phase 2 dose was established as a fixed dose of 200 mg IV Q3W.

1.4.4.2. BGB-A317_Study_001 Phase 1b

As of 13 January 2017, 189 patients with solid tumors had received BGB-A317 treatment in Phase 1b across 9 expansion cohorts in BGB-A317_Study_001. The median duration of treatment for the combined subject population was 64 days (range: 1 to 235 days).

The most commonly occurring treatment-emergent adverse events (TEAEs) were fatigue (22%), nausea (18%), decreased appetite (14%), vomiting (14%), diarrhoea (13%), and constipation (12%). Grade 3 or higher TEAEs occurring in more than 3 patients included vomiting (n=5), pneumonia (n=5) anaemia (n=4), and ascites (n=4).

Treatment-emergent AEs assessed as related to BGB-A317 reported ≥ 5% of patients included fatigue (9%), rash (5%), nausea (5%), and diarrhoea (5%). Eleven patients experienced ≥ Grade 3 TEAEs related to BGB-A317. These events included nausea (n=1), diarrhea (n=2), colitis (n=2), stomatitis (n=1), fatigue (n=1), mucosal inflammation (n=1), pneumonitis (n=3), and hyperthyroidism (n=1). Some patients experienced more than one ≥ Grade 3 TEAE considered related to BGB-A317.

Twenty patients (11%) experienced a TEAE that led to treatment discontinuation; Grade 3 or higher TEAE were reported in 18 of these 20 patients. Treatment-emergent AEs leading to treatment discontinuation reported in at least 2 patients included pneumonitis (n=3) and vomiting (n=2). All other TEAEs that led to treatment discontinuation occurred in single patients.

Nineteen patients (10%) experienced an immune-related AE (irAE). The most frequently occurring irAEs included pneumonitis (n=4); aspartate aminotransferase (AST) increased, hyperthyroidism, and rash (3 patients each); and colitis, dermatitis, diarrhoea, and hypothyroidism (2 patients each). All other irAEs occurred in single patients. Eight of these 19 patients (42%) experienced a ≥ Grade 3 irAE.

Preliminary efficacy results indicate 6 patients achieved confirmed partial response (PR) to BGB-A317 monotherapy and 55 patients had stable disease (SD).

1.5. Study Rationales

1.5.1. Rationale for BGB-A317 in the Treatment of Hepatocellular Carcinoma

High levels of FcγR-expressing myeloid derived cells (eg, M2 macrophage, MDSC) in tumor tissues predict a poor survival of tumor-bearing animals after anti-PD-1 monoclonal antibody treatment; this is possibly due to Fc-FcγR-mediated ADCC or antibody-dependent cellular phagocytosis (ADCP) depletion of effector T-cells (Gul et al, 2015; Prieto et al, 2015; Makarov-Rusher et al, 2015; Beers et al, 2016; Dahan et al, 2015). As a no-to low-FcγR-binding agent (thus causing minimal ADCC/ADCP effect), BGB-A317 is expected to potentially show superior efficacy and lower toxicity in hepatocellular carcinoma. Available data from a clinical trial with another anti-PD-1 monoclonal antibody, nivolumab, has shown the drug to have both a manageable safety profile and promising antitumor activity in patients with unresectable HCC (Section 1.1).

According to the latest data collected from the Phase 1 BGB-A317_Study_001, BGB-A317 monotherapy has established a manageable safety profile, with the most common side effects consistent with known class effects of other anti-PD-1 antibodies (Section 1.6). As of the data cutoff date (28 April 2017), a small cohort of heavily pretreated patients with HCC (n=27 evaluable; n=40 enrolled) were treated with BGB-A317 5 mg/kg Q3W in Phase 1B of BGB-A317_Study_001. Two patients with confirmed PR and one with unconfirmed PR were observed. It is important to note that the median duration of follow-up in this cohort of HCC patients was only 64 days. Responses were assessed after every 9 weeks on therapy with confirmation of response occurring at least 4 weeks after initial response assessment. Twenty-five patients remain on study treatment.

1.5.2. Rationale for Selection of BGB-A317 Dose

The fixed dose of BGB-A317 200 mg was selected based on both nonclinical studies and available clinical data (efficacy, safety, and PK).

The safety of BGB-A317 has been tested across a range of doses in BGB-A317_Study_001 (0.5 mg/kg to 10 mg/kg Q2W [n=62]; 2 mg/kg to 5 mg/kg Q3W [n=41]) with no MTD defined at the highest dose examined. Efficacy has also been demonstrated in 23 of 266 (9%) evaluable patients to date, diagnosed with a variety of tumor types and treated according to a scheduled dose range. Specifically, rates of treatment-related AEs and serious adverse events (SAEs) observed in patients taking 2 mg/kg and 5 mg/kg Q2W and Q3W were comparable suggesting no clear dose dependence across these regimens. Similarly, confirmed objective response rates (ORRs) in patients treated with 2 mg/kg and 5 mg/kg Q2W ranged between 5% and 14%, compared to a range of 17% to 37% for patents treated at 2 mg/kg and 5 mg/kg Q3W.

According to Phase 1a component PK data, serum concentrations of BGB-A317 showed linear relationships with doses ranging from 0.5 mg/kg Q2W to 10 mg/kg Q2W. Because the clearance of BGB-A317 was found to be independent of body weight, a 200-mg dose (body-weight adjusted dose between 3 and 4 mg/kg) administered Q3W was expected to lead to serum exposure between 2 mg/kg and 5 mg/kg. This prediction was corroborated with simulations conducted using the population PK analysis and further supported by preliminary PK data from 5 patients who received 200 mg Q3W (Phase 1a, part 3). BGB-A317

concentrations after the first 200-mg dose was in between the concentrations observed after 2 mg/kg and 5 mg/kg doses (in patients from Phase 1a, parts 1, 2). Additionally, as shown by available data from BGB-A317_Study_001 and BGB-A317-102, the PK profile of BGB-A317 is consistent between Chinese patients and Caucasian patients.

Additionally, no unexpected treatment-related AEs occurred in the 200 mg fixed-dose cohort (Phase 1a, Part 3) when compared to body-weight-based cohorts. Of the evaluable patients treated (n=4), 1 patient had a best overall response (BOR) of SD and 3 patients had BORs of progressive disease (PD). Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving BGB-A317 200 mg Q3W.

In conclusion, BGB-A317 200 mg Q3W is the recommended dose for this Phase 2 global study.

1.6. Benefit-Risk Assessment

Patients with previously treated unresectable HCC who have progressed after 1-2 prior lines of therapy represent a population with a great unmet medical need. Sorafenib is currently the only approved systemic therapy available to patients with HCC in the first-line setting worldwide that has a manageable safety profile (characterized by a relatively moderate incidence of dose reductions or drug discontinuations; see Section 1.1). More recently, regorafenib was approved for the treatment of HCC patients who have progressed after sorafenib treatment in the US, EU, and Japan (see Section 1.2).

Data from a Phase 1/2 clinical trial of nivolumab, a similar anti-PD-1 antibody, indicated an objective response of 20% (95% CI: 15% to 26%) that is durable, which suggests the potential efficacy of anti-PD-1 antibody for the treatment of patients with advanced HCC (for additional discussion, see Section 1.1). In a small cohort of patients (n=20, evaluable) with HCC in the second-line setting treated with BGB-A317 5 mg/kg in Phase 1b of BGB-A317_Study_001, confirmed PRs were observed in 2 patients with another patient who had unconfirmed PR and continued on treatment. These encouraging results occur in patients with a median treatment of 64 days, and responses were assessed after every 9 weeks on therapy. Confirmation of response was required and occurred at least 4 week after initial response assessment. A majority of patients (25 of 40, 62.5%) remain on treatment (Yen et al, 2017)

More than 400 patients have been treated with BGB-A317 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 3/4 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 BGB-A317, please refer to the Investigator's Brochure.

Given the unmet medical need and limited treatment options in this indication, the benefit/risk assessment based on available BGB-A317 Phase 1 data and the publication from Phase 1/2 study of nivolumab is considered favorable. This Phase 2 study will be conducted in order to assess the potential benefit and safety of BGB-A317 monotherapy in unresectable HCC patients who have received at least 1-2 lines of prior therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of BGB-A317 through Independent Review Committee (IRC) assessed ORR by Response Evaluation Criteria in Solid Tumors (RECIST) Version (v)1.1 in previously treated, unresectable HCC.

2.1.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To assess the efficacy of BGB-A317 through duration of response (DOR), progression-free survival (PFS), disease control rate (DCR) and clinical benefit rate (CBR) assessed by IRC and OS
- To assess efficacy of BGB-A317 through ORR, DOR, PFS, DCR, and CBR assessed by the investigators
- To assess the safety and tolerability of BGB-A317 in patients with previously treated unresectable HCC
- To assess the health-related quality of life (HRQoL) of BGB-A317 in patients with previously treated unresectable HCC

2.1.3. Exploratory Objectives

The exploratory objectives of the study are:

- To assess potential predictive biomarkers
- To characterize the PK of BGB-A317
- To assess host immunogenicity to BGB-A317

2.2. Study Endpoints

2.2.1. Primary Endpoint

The primary endpoint is ORR (CR + PR) based on RECIST v 1.1 in patients with previously treated unresectable HCC as evaluated by an IRC.

2.2.2. Secondary Endpoints

- DOR, PFS, DCR and CBR assessed by IRC, and OS
- ORR, DOR. PFS, DCR and CBR assessed by investigators
- Safety and tolerability assessment of AEs, SAEs, physical examination, vital signs, ECG, and laboratory measurements
- HRQoL measured using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Hepatocellular Carcinoma 18 Questions (EORTC QLQ HCC18) index score, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

(EORTC QLQ-C30) index-score, and 5-level version of the European Quality of Life 5-Dimensional Questionnaire (EQ-5D-5L)

2.2.3. Exploratory Endpoints

- A predictive biomarker (for example, PD-L1 expression and gene expression profiling in tumor tissue)
- Pharmacokinetics: summary of plasma concentrations of BGB-A317
- Immunogenicity: assessments of immunogenicity of BGB-A317 to determine the incidence of anti-drug antibodies (ADAs)

3. STUDY DESIGN

3.1. Summary of Study Design

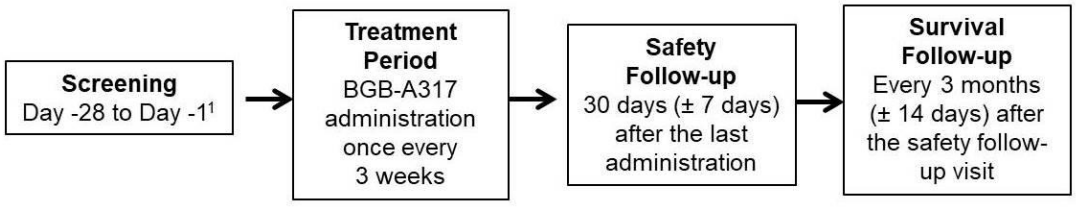
This is a Phase 2, multicenter, open-label study in adults with previously treated unresectable HCC. Patients will receive open-label BGB-A317 200 mg intravenously (IV) Q3W. Each treatment cycle will be 21 days in duration. Study treatment is to be continually administered until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the opinion of the investigator, the patient is no longer benefiting from study therapy, whichever should occur first.

The study procedures will occur over a Screening phase of up to 28 days, a Treatment phase, a Safety Follow-up phase and a Survival Follow-up phase. See Section 3.3 for a description of each phase. For all study procedures see Section 7 and Appendix 1.

3.2. Study Schematic

The study design schematic is presented in Figure 1. Approximately 228 patients will receive open-label BGB-A317. Of the 228 patients, at least 100 patients will be enrolled who have had no more than 1 line of prior systemic therapy and at least 100 patients will be enrolled who have had at least 2 lines of prior systemic therapy (see Appendix 10 for additional guidance).

Figure 1: Study Design Schematic



[1] Screening assessments will be completed within 28 days prior to the first dose of the study drug. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed before study drug administration.

3.3. Duration of Study

Total duration of study participation will vary by patient. Each study phase is further discussed below.

3.3.1. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of BGB-A317. Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure. Patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms should undergo pulmonary function testing (refer to Section 7.1.4 and Appendix 1 for details). Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

A fresh baseline biopsy sample (if accessible and appropriate) and archival tumor tissue (if available) are required for biomarker analysis. Refer to Section 7.8 for details.

3.3.2. Treatment Period

After completing all Screening activities, patients confirmed by the sponsor to be eligible will receive open-label treatment with BGB-A317 200 mg IV Q3W until intolerable toxicity, withdrawal of informed consent, or the time point at which, in the investigator's opinion, the patient is no longer benefiting from study therapy, whichever should occur first. Treatment beyond initial disease progression (as assessed by the investigator per RECIST v1.1) is permitted, provided the patient meets the criteria in Section 7.5.

Radiological assessment of tumor-response status should be performed every 6 weeks in the first 18 weeks then every 9 weeks thereafter. Tumor response will be assessed by an Independent Review Committee (IRC) and by investigators. Details are provided in Section 7.5.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v 4.03), and laboratory abnormalities. Vital signs, physical examinations, ECOG PS change, and electrocardiogram (ECG) results will also be used for safety assessment. Safety assessments are further detailed in Section 7.4 and the Schedule of Assessments (Appendix 1).

3.3.3. Safety Follow-up Period

Patients will return approximately 30 days after the last dose of study drug or before the initiation of a new anticancer therapy (whichever occurs first) for a Safety Follow-up visit to collect AEs or SAEs that may have occurred after the patient discontinued from the study treatment. All irAEs will be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation (see Section 7.11).

3.3.4. Survival Follow-up Period

Patients who discontinue study drug for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.5 and the Schedule of Assessments (Appendix 1), until

disease progression, withdrawal of consent, death, or start of a new anticancer therapy, whichever occurs first (see Section 7.12).

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

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 informed consent form (or acceptable age according to local regulations)
3. Patients must meet the following criteria:
    a. Histologically confirmed HCC
    b. Patients with BCLC stage C, BCLC stage B not amenable to locoregional therapy or relapsed after locoregional therapy, and not amenable to a curative treatment approach (Appendix 11)
    c. Child-Pugh A (Appendix 2)
    d. Has received at least 1 line of systemic therapy for unresectable HCC (must have progressed on or is intolerant to, in the first-line setting, either sorafenib, chemotherapy, or an experimental therapy that has demonstrated efficacy in a Phase 3 study [eg, lenvatinib]; see Appendix 10 for additional guidance)
4. Has at least 1 measurable lesion as defined per RECIST v1.1
5. Has ECOG PS ≤ 1
6. If patient has HBV, meets the following criteria as applicable to the infection type:

    For patients with inactive/asymptomatic carrier, chronic, or active HBV:

    - Has HBV deoxyribonucleic acid (DNA) < 500 IU/mL (or 2500 copies/mL) at Screening

    Note: Patients with detectable hepatitis B surface antigen (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 enrollment and should continue treatment for 6 months after study drug treatment discontinues.
7. Has adequate organ function as indicated by the following laboratory values:
    a. Absolute neutrophil count (ANC) ≥ 1500/mcl, platelets ≥ 60000/mcl, hemoglobin ≥ 85 g/L or 5.3 mmol/L; Note: Patients must not have required a transfusion of blood product or growth

factor support within the 14 days before sample collection

b. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 9)

c. Serum total bilirubin ≤ 34.2 µmol/L (2 mg/dL)

d. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.7 × upper limit of normal (ULN)

e. Activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 5 × ULN

g. Serum albumin ≥29 g/L

8. Females of childbearing potential (as defined in Section 7.1.2.1**)** must be willing to use a highly effective method of birth control for the duration of the study, and for at least 120 days after the last dose of BGB-A317, and have a negative urine or serum pregnancy test within 7 days of the first study drug administration
9. Non-sterile males (as defined in Section 7.1.2.2) must be willing to use a highly effective method of birth control for the duration of the study and for at least 120 days after the last dose of BGB-A317
10. Must be willing to abstain from alcohol consumption while receiving BGB-A317

4.2. Exclusion Criteria

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

1. Has known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
2. Prior therapies targeting PD-1 or PD-L1
3. Has known brain or leptomeningeal metastasis
4. Has received within 4 weeks before enrollment locoregional therapy to the liver (ie, transarterial chemoembolization, transcatheter embolization, hepatic arterial infusion, radiation, radioembolization, or ablation)
5. Has received:
    a. Within 28 days or 5 half-lives (whichever is shorter) of the first study drug administration: any chemotherapy, immunotherapy (eg, interleukin, interferon, thymoxin) or any investigational therapies
    b. Within 14 days of the first study drug administration: sorafenib, regorafenib, or any Chinese herbal medicine or Chinese patent medicines used to control cancer
6. Has tumor thrombus involving main trunk of portal vein or inferior vena cava
7. Has at screening and/or has any prior history of ≥ Grade 2 hepatic encephalopathy (Appendix 2)
8. Has, at screening, pericardial effusion, uncontrollable pleural effusion, or clinically significant ascites defined as meeting either of:
    a. Detectable ascites on screening physical examination OR
    b. Has at screening, ascites requiring paracentesis
9. 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. Type I 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

10. Has any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication within 14 days before study drug administration

    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)

11. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
12. Has a known history of HIV infection
13. Has undergone prior allogeneic stem cell transplantation or organ transplantation
14. Has any of the following cardiovascular risk factors:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, within 28 days before the first study drug administration
    b. Symptomatic pulmonary embolism within 28 days before the first study drug administration
    c. Any history of acute myocardial infarction within 6 months before the first study drug administration
    d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) within 6 months before the first study drug administration
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity within 6 months before administration of study drug(s)
    f. Any history of cerebrovascular accident within 6 months before the first study drug administration

15. Has a history of severe hypersensitivity reactions to other monoclonal antibodies
16. 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)
17. Has been administered a live vaccine within 28 days 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.

18. Underlying medical conditions 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 (AEs); or insufficient compliance during the study according to investigator's judgement.
19. Concurrent participation in another therapeutic clinical trial or enrollment in a prior BeiGene trial for the treatment of HCC
20. Prior malignancy active within the previous 2 years except for tumor for which a subject is enrolled in the study, and locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. BGB-A317

BGB-A317 is a monoclonal antibody 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. BGB-A317 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. BGB-A317 must be stored at temperatures between 2 and 8^{o}C and protected from light.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Investigator's Brochure for other details regarding BGB-A317.

5.2. Dosage, Administration, and Compliance

BGB-A317 200 mg will be administered by the investigator or designee on Day 1 of each 21-day cycle Q3W.

BGB-A317 will be administered by IV infusion, preferably using a volumetric pump 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.

As a routine precaution, after infusion of BGB-A317 on day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 1 hour afterwards in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (Cycle 1, Day 1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. BGB-A317 must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of irAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 7.

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

5.3. Overdose

Any overdose (defined as ≥ 600 mg of BGB-A317 in a 24-hour period) or incorrect administration of study drug should be noted on the study drug administration electronic case report form (eCRF). All AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours of awareness via SAE reporting process as described in Section 8.7. Supportive care measures should be administered as appropriate.

5.4. Investigational Medicinal Product Accountability

BGB-A317, the investigational medicinal product (IMP), will be provided by the sponsor. The investigational site will acknowledge receipt of IMP. Any damaged shipments will be replaced.

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

5.5. Dose Delay and Modification

Every effort should be made to administer the study drug according to the planned dose and schedule Q3W from Cycle 1 Day 1. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.5.1. Dose Modification for BGB-A317

There will be no dose reduction for BGB-A317 in this study. Delays less than 12 weeks will be permitted. Investigators should make every effort to maintain dose intensity in patients.

Patients may temporarily suspend study treatment if they experience toxicity that is considered related to BGB-A317 and requires a dose to be withheld. The patients should resume BGB-A317 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 BGB-A317. The investigator should discuss with the sponsor medical monitor or designee to determine the subsequent dosing visits. If the patient is unable to resume BGB-A317 within 12 weeks after the last dose of BGB-A317, then the patient should be discontinued from 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.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date (refer to the visit window in Appendix 1), with the subsequent visit conducted according to the planned schedule Q3W from Cycle 1 Day 1.

Management of BGB-A317 irAEs and infusion-related reactions are described in Appendix 7 and Appendix 8, 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 the supportive care (eg, anti-emetics, antidiarrheals) 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 medications received within 30 days before the first dose of study treatment and 30 days after the last infusion of study drug should be recorded.

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

BeiGene does not require patients with active hepatitis C to receive treatment with antiviral therapy. Patients with detectable HCV RNA and who are receiving treatment at screening should remain on continuous, effective antiviral therapy during the study. Investigators can consider treatment with sofosbuvir alone or in combination with other antivirals following the AASLD guideline (https://www.hcvguidelines.org) 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 first dose.

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 7) and be at nonimmunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) before the next BGB-A317 administration. 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 for a non-malignant indication.

Palliative (limited-field) radiation therapy should not have been administered within 4 weeks before enrollment.

On-study palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with sponsor medical monitor to ensure study compliance, and sponsor medical monitor 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 to rule out progression of disease

6.1.2. Prohibited or Restricted Concomitant Medications

The following medications are prohibited or restricted at the time of screening and during the administration of BGB-A317:

- Immunosuppressive agents (except to treat a treatment-emergent drug-related AE)
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except to treat a treatment-emergent 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)
- Extensive radiation therapy, except for local, palliative radiation therapy to bone (described in Section 6.1.1)
- Live vaccines within 28 days prior to the first dose of study drug and 60 days following the last dose of study drug
- 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.

The following guidelines should also be followed during the study:

- With the exception of diagnostic biopsy of tumor tissue or placement of a venous access device, the investigator should discuss with the sponsor medical monitor any patient who requires surgery during the study
- Patients should avoid alcohol completely and should avoid other addictive drugs during the study. However, Opiates and other medications required for palliative management of patients are allowed.
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function including Child Pugh-A classification should be carefully monitored. Patients must notify the investigator of all concurrent medications used during the study

6.2. Potential Interactions Between BGB-A317 and Concomitant Medications

The potential for drug-drug interaction between the study drugs (BGB-A317) and small-molecule drug products is very low, given BGB-A317 is therapeutic monoclonal antibody. Because BGB-A317 is 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 and eCRF for each patient.

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

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be rescheduled for the next feasible date (the visit window is provided in Appendix 1), with the subsequent visit conducted according to the planned schedule Q3W from Cycle 1 Day 1.

7.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose of study drug. Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure.

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 undergo pulmonary function tests (refer to Appendix 1 for details).

Patients who have, within 6 months before first study drug administration, any clinical evidence of portal hypertension with bleeding esophageal or gastric varices, or those that have undergone any major surgical procedure within 28 days before first study drug administration, should be considered to have a serious underlying medical condition that would be unfavorable for the administration of study drug.

Screening evaluations may be repeated as needed within the screening period; the investigator will assess patient eligibility according to the latest screening assessment results.

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

Re-screening under limited conditions may be allowed after consultation with the sponsor, provided missing a criterion is not due to a rapidly deteriorating condition or PD. Re-screening is allowed only once. Re-screened patients must sign a new ICF and will receive a new screening number.

Procedures conducted during the screening visit only are described in this section. For the description of other assessments that are conducted during screening, as well as throughout the study, refer to the following sections: Safety Assessments (Section 7.4), Tumor and Response Evaluations (Section 7.5) and Biomarkers (Section 7.8).

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 (ie, presence or absence); 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. If appropriate, clinically significant disease should be graded according to NCI-CTCAE v 4.03 and reported in the eCRFs.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior loco-regional therapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. In particular, information may include but is not limited to collection of source documentation regarding prior systemic treatment for HCC, response to therapy, and duration of response. Radiographic studies performed prior to study entry may be collected for review by the investigator.

7.1.2. Females of Childbearing Potential and Contraception

7.1.2.1. 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 (applicable to both study participants and sexual partners of male participants).

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)
- Post-menopausal, 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 all alternative medical causes for lack of spontaneous menstruation considered, AND a follicle-stimulating hormone concentration measurement in the postmenopausal range (≥ 30 IU/mL) drawn in patients who are not using hormone replacement therapy or any form of hormonal contraception method

7.1.2.2. Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2014). 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, implantable
    - Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide
- An intrauterine device
- Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner
    - Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success
    - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, 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 used in combination with one of the highly effective forms of birth control listed above.

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 receiving study drug. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.4. Pulmonary Function Tests

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 or designee will verify, the eligibility of each patient. All screening procedure results and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may apply. An Inclusion/Exclusion checklist will be reviewed by the sponsor or designee who will provide approval before enrollment. No eligibility waivers will be granted.

7.2.2. Patient Numbering

Each patient enrolled in this study will receive a unique identification number after signing the ICF. Patient numbers will be assigned in chronological order by site. Once an identification number has been assigned to a patient, it cannot be reassigned to any other patient. Re-screened patients will sign a new ICF and receive a new identification number.

7.3. BGB-A317 Dispensation

BGB-A317 will be dispensed and administered as described in Section 5.2.

7.4. Safety Assessments

7.4.1. Vital Signs

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

To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. If blood pressure is >150/100 mmHg in a patient without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

7.4.2. Physical Examinations

A 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. Any abnormality identified at baseline 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 in patient notes. New or worsened clinically significant abnormalities are to be recorded as AEs on the Adverse Event eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.4.3. Eastern Cooperative Oncology Group Performance Status

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

7.4.4. Laboratory Safety Tests

Local or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 4. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed prior to treatment authorization. Hematology and serum chemistry (including liver function tests) as specified in Appendix 4

should be performed weekly for the first 3 cycles and at the beginning of subsequent cycles. After Cycle 1, results are to be reviewed within 2 days before study drug administration.

Furthermore, the following tests will be performed as specified in Appendix 1:

- Urine or serum pregnancy test (for women of childbearing potential, including premenopausal women who have had a tubal ligation; refer to Section 7.1.2 for additional information)
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- Hepatitis serology and viral load
    - Hepatitis B surface antigen (HBsAg), antibodies against HBsAg, hepatitis B core antibody (HBcAb)
    - Hepatitis C virus (HCV) serology (anti-HCV)
    - Hepatitis B virus (HBV) deoxyribonucleic acid (DNA) and HCV ribonucleic acid (RNA)
- Alpha fetoprotein biomarker assessment

Details about sample collection and shipment will be provided in a separate instruction manual.

7.4.5. Electrocardiograms

Twelve-lead ECG recordings are required at screening and as clinically indicated. When coinciding with blood draws, ECG assessment should be performed prior to blood draws. All ECG recordings should be performed after the patient has been resting in a semi-recumbent position for at least 10 minutes, and a repeat ECG should be performed to confirm findings, if any.

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

7.4.6. Adverse Events

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, v 4.03 (NCI-CTCAE, June 2010). Characterization of toxicities will include severity, duration, and time to onset (see Section 8.3).

All AEs, including SAEs, will be collected as described in Section 8.6. At the end of treatment, ongoing AEs considered related to study treatment will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the AE.

7.4.7. Ophthalmologic Examination

Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed by an appropriate specialist (eg, ophthalmologist) 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 first study drug administration 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 after the last dose of study treatment.

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

7.5. Tumor and Response Evaluations

Tumor imaging will be performed within 28 days prior to the first study treatment. Results of standard of care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to study drug administration may be used for the purposes of screening rather than repeating the standard of care tests. Patients must have at least one (1) measurable lesion according to RECIST v1.1 at baseline, provided that:

- 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

During the study, tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first 18 weeks and approximately every 9 weeks (± 7 days) thereafter. Investigators may perform additional assessments if clinically indicated.

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.). MRI may be used when it is the standard of care at a site, regardless of whether or not CT is contraindicated.

The liver should be imaged using tri-phasic scans (ie, late arterial phase, portal venous phase and delayed/equilibrium phase are required). Every effort should be made to keep the methodology consistent across visits for a subject (ie, phases acquired, timing for each phase, etc). Scanning details will be provided by the imaging vendor in a separate site manual.

- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a noncontrast 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, or if clinically indicated, TC-99m or NaF-PET bone scans should be repeated when a complete response (CR) is suspected in target lesion or when progression in bone is suspected.

- CT scans of the neck or extremities should also be performed if clinically indicated and followed throughout the study, if there is evidence of metastatic disease in these regions at screening. At the investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

For subsequent tumor assessments, the same radiographic procedure used to assess disease sites at screening are required to be used throughout the study (eg, the same contrast protocol for CT scans). Imaging of the head is not required during subsequent tumor assessment if tumor was not detected at baseline. All known sites of disease must be documented at screening and reassessed at each subsequent tumor evaluation.

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 5). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

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

For immune therapies such as BGB-A317, 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 for PD suspected by the investigator as pseudoprogression, the following criteria must be met in order to treat patients continuously until PD is confirmed by repeated imaging at least 4 weeks later but not exceeding 6-8 weeks from the date of initial documentation of PD:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤ 1
- Absence of rapid progression of disease or of progression at a critical anatomical site (eg, progression of a spinal lesion with impending cord compression) that necessitates 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

Patients with radiographic disease progression that is confirmed at a subsequent tumor assessment may be considered for continued BGB-A317 treatment in agreement with the sponsor medical monitor if they continue to meet the criteria above and have evidence of clinical benefit. The decision to continue study drug beyond initial investigator-assessed progression must be discussed with the sponsor medical monitor and documented in the study records. The patient must sign an ICF for continued treatment beyond RECIST v1.1 progression.

Patients who discontinue study treatment 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, dies, or until the study terminates, whichever occurs first.

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

7.6. Health-Related Quality of Life Assessment

Patients will be asked to complete the EORTC QLQ-C30, EORTC QLQ-HCC18, and EQ-5D-5L questionnaires, before any clinical activities are performed, during on-study clinic visits according to the schedule in Appendix 1. The questionnaires will be provided in the patient's preferred language.

7.7. Pharmacokinetic and Anti-Drug Antibody Testing

Pharmacokinetic samples will be collected at the time points presented in Appendix 1. Procedures for collection of PK samples are described in the laboratory manual. Predose (within 60 minutes before starting infusion) samples are required to be collected at Day 1 of Cycles 1, 2, 5, 9 and 17; 2 postdose (within 30 minutes after completing BGB-A317 infusion) samples are required to be collected at Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the mandatory Safety Follow-up Visit. All trough samples should be drawn at the same time as blood collection for anti-BGB-A317 antibodies. Should a subject present with a ≥ Grade 3 irAE (refer to Section 8.7), additional blood PK samples will be taken to determine the plasma concentration of BGB-A317.

BGB-A317 may elicit an immune response. Patients with signs of any potential immune response to BGB-A317 will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study (see Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Koren et al, 2008; Worobec and Rosenberg, 2004a; Worobec and Rosenberg, 2004b) to characterize ADA responses to BGB-A317 in support of the clinical development program.

7.8. Biomarkers

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

Archival tumor tissues (formalin-fixed paraffin-embedded block or 5-10 unstained slides) are required (if available) for biomarker analysis. A fresh tumor biopsy at baseline (if accessible and appropriate) if archival tissue is not available is recommended. In addition to PD-L1 expression, other exploratory predictive biomarkers, such as gene expression profiling, that are related to response or clinical benefit of BGB-A317 may also be evaluated. 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.

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.

7.9. Visit Windows

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

be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with the subsequent visit performed according to the planned schedule Q3W from Cycle 1 Day 1.

7.10. Unscheduled Visits

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

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

7.11. Safety Follow-up Visit

Patients who discontinue treatment for any reason will be asked to return to the clinic for a Safety Follow-up visit within 30 days (± 7 days) after the last dose of study drug. In addition, telephone contacts with patients should be conducted to assess irAEs and concomitant medications at 90 days (± 14 days) after the last dose of study drug, regardless of whether or not the patient starts a new anticancer therapy.

After 90 days, investigators should report any SAEs or AEs that are believed to be related to study drug if they become aware of them. Patients who discontinue study drug due to a drug-related AE will be followed until the resolution of the AE (to Grade 0-1, baseline, stabilization) or initiation of a new treatment, whichever comes first.

Any End of Treatment (EOT) visit at which a response assessment showed progressive disease, resulting in patient discontinuation, may be used as the Safety Follow-up visit, if appropriate. If the interval between the EOT visit and the Safety Follow-up visit is less than 7 days, the EOT visit can be delayed and combined with the Safety Follow-up visit. Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.5.

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

7.12. Survival Follow-up

Following discontinuation of the study treatment, all patients will be followed for survival status beginning 3 months (± 14 days) after the Safety Follow-up visit or as directed by the sponsor. Information on survival follow-up and the subsequent anticancer treatment will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) until death, loss to follow-up, withdrawal of consent, or study termination by the sponsor, whichever occurs first.

7.13. Patient, Treatment, Study, and Site Discontinuation

Patients who discontinue study treatment, but who have not withdrawn consent for follow-up, should be followed for assessments of antitumor activity (Section 7.5), safety (Section 7.4) and survival (Section 7.12), if possible.

7.13.1. Discontinuation from Study Treatment

Patients have the right to voluntarily withdraw from the study or 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 should be followed for assessments of antitumor activity, safety, and survival, if possible.

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 may 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

Patients will be permitted to continue study drug(s) if pseudoprogression is suspected and/or there is a reasonable belief that the patient could derive benefit from study drug after RECIST v1.1 criteria for PD are met provided they meet all criteria specified in Section 7.5. The decision to continue study drug(s) beyond initial investigator-assessed progression must be discussed with the sponsor's medical monitor and documented in the study records.

7.13.2. End of Study

Study termination is defined as the time point when data collection for the patient will stop. The study will continue until the last patient has died, becomes lost to follow up, or withdraws from study, or until sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

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

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

Patients who, in the opinion of the Investigator, continue to benefit from tislelizumab at study termination, will be offered the option to continue treatment in a company-sponsored clinical trial until it is commercially available in the country. 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)

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-A317

BGB-A317 is an investigational agent that is currently in clinical development. Limited safety data are available in patients and the full safety profile has not been characterized. The following recommendation is based on results from nonclinical and clinical studies with BGB-A317 and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. A summary of AEs observed with anti-PD-1 therapy is 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. Guidance for evaluation and management of suspected irAEs are provided in Section 8.7.3 and Appendix 7.

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 trial. Results from the nonclinical toxicology studies and clinical data with BGB-A317, as well as the nonclinical/clinical data from other

PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, patients who have undergone allogenic stem cell or organ transplantation, and patients who have received a live viral vaccine within 28 days before study drug administration, are excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. 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-A317. Administration of BGB-A317 will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

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

All irAEs should be recorded until up to 90 days after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation.

Investigators are instructed to report all events (including AEs and pregnancy-related AEs). In addition, the sponsor medical monitor or safety physician will review and evaluate observed AEs on a regular basis.

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 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 8.6.2.3.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the BGB-A317 Investigator’s Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes 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, otherwise the event should be assessed as not related:

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

8.3.4. Following Adverse Events

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

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

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

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a

recognized follow-up period, the sponsor will be provided with a copy of any post-mortem findings, including histopathology.

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

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, hematology, 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 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 a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of an SAE/serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Investigator's Brochure.

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

8.6.1. Adverse Event Reporting Period

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

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until either 30 days after last dose of study treatment or initiation of new anticancer therapy, whichever occurs first. All irAEs should be reported for 90 days after the last dose of BGB-A317, regardless of whether or not the patient starts a new anticancer therapy. After this period, the investigator should continue to report any SAEs that are believed to be related to BGB-A317 treatment.

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 (Grade 3 or worse), the event must be reported promptly to the sponsor or designee as described in Table 1.

Table 1. Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method
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 Table 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.

In case the electronic data capture (EDC) system is nonoperational, facsimile transmission of the paper SAE form will be used to transmit this information. After the EDC system becomes operational again, the investigator must enter the SAE information there.

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. 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.

This protocol is being conducted under an Investigational New Drug (IND) with the US FDA. All IND safety reports, including SUSARs (as defined in Section 8.5), submitted to the FDA will also be sent to all investigators conducting studies under this IND. When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

8.6.3. Eliciting Adverse Event Information

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 (prescribed, over-the-counter, herbal or other supplements) 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 identifies the disease progression should be reported as the AE term. For instance, 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.

If there is any uncertainty regarding whether a SAE is due to disease progression, it should be reported as an AE.

8.6.5. Recording Deaths

When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. 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 BGB-A317, 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 or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

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

8.6.7. Recording Post-Study Adverse Events

A post-study 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 discharged 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 document:

- BGB-A317 Investigator's Brochure

8.7. Management of Adverse Events of Special Interest

As a routine precaution, after infusion of BGB-A317 on Day 1 of Cycle 1 and Cycle 2, patients must be monitored for at least 1 hour afterwards in an area with resuscitation equipment and emergency agents.

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

8.7.1. Abnormal 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 guidelines for suspected infusion-related reactions due to BGB-A317 are provided in Appendix 8.

8.7.2. Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

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

8.7.3. Immune-Related Adverse Events

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

Diagnostic evaluation and management of irAEs is based on recent 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 7.

A list of potential irAEs appears in Table 2. All conditions similar to those listed should be evaluated to determine whether they are immune-related. Suggested diagnostic testing is presented in more detail in Appendix 7 for select AEs. For any AEs not included in Appendix 7, please refer to the ESMO and ASCO guidelines (Haanen et al, 2017, Brahmer et al 2018) for further guidance on management or treatment.

Table 2. Immune-Related Adverse Events Associated with Anti-PD1 Drugs

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

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase;
PD-1, programmed cell death protein-1.

8.7.4. Hepatic and Renal Function Abnormalities

Patients with advanced HCC generally have underlying cirrhosis with decreased hepatic function. Special attention is needed because they may also have a concomitant chronic viral infection. Therefore, when a hepatic event, such as liver function laboratory abnormalities, is observed, the Investigator must evaluate for re-activation of viral hepatitis, consider other drug-related toxicity, and exclude PD involving the liver. For diagnosis and management of patients with AST or ALT values ≤ Grade 1 at baseline, please see Section 8.7.3 and refer to Appendix 7.

In patients with Grade 2 AST/ALT abnormalities at baseline, therapeutic interventions with a steroid treatment may be required with rising AST and ALT laboratory abnormalities. The following algorithm is proposed for the use of steroid treatment:

- If AST or ALT increases by ≥ 50% relative to baseline and lasts for at least 1 week, start oral prednisolone 1 mg/kg/day and taper over at least 2-4 weeks; re-escalate dose if liver function tests (LFTs) worsen, depending on clinical judgement (manage as per Appendix 7). Study treatment should be held until AST/ALT increase resolved/improved to baseline and prednisolone tapered to ≤ 10 mg.
- If any ALT or AST increases meets Grade 3 criteria, initiate steroid therapy promptly per Appendix 7. Study treatment will be held until AST or ALT improves to value ≤ Grade 2. Study drug may be reintroduced only after discussion with the Sponsor.
- If any ALT or AST increases meets Grade 4 criteria, initiate steroid therapy promptly per Appendix 7. Study treatment will be discontinued permanently

Renal Function Abnormalities

Patients with moderate renal dysfunction (estimated glomerular filtration rate > 30 mL/min/1.73m^2 and < 60mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration equation) may be enrolled into the study (Appendix 9). The following algorithm is proposed for the use of steroid treatment in the management of immune-related adverse events:

- If the serum creatinine is normal at baseline, please see Section 8.7.3 and refer to Appendix 7 for diagnosis and management of patients with abnormal renal laboratory values.
- If the serum creatinine is Grade 1 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 2 after starting treatment with BGB-A317, refer to Appendix 7 for diagnosis and management of patients with abnormal renal laboratory values. Check the eGFR using Appendix 9 and the eGFR calculator link. In the setting of a Grade 2 serum creatinine increase only, study treatment can continue unless the serum creatinine increases by at least 50% from the baseline value OR the eGFR falls below 20 mL/min.
- If the serum creatinine is Grade 2 at baseline and increase in serum creatinine meets criteria for serum creatinine increase ≥ Grade 3 after starting treatment with BGB-A317, refer to Appendix 7 for diagnosis and management of patients with abnormal renal laboratory values. In the setting of a Grade 3 serum creatinine increase only, study treatment will be held until serum creatinine improves to baseline and treatment may resume only after discussion with Sponsor Medical Monitor.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

9.1. Statistical Analysis

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® v 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.

The following descriptive statistics will be used to summarize the trial data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, median, minimum, and maximum
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of non-missing observations (N), median, minimum and maximum. Kaplan-Meier (KM) event rates may also be provided if applicable for specific time to event variables

9.1.1. Analysis Sets

The Safety Population (SAF) includes all patients who have received any dose of BGB-A317. It will be the primary population for efficacy and safety analysis.

The Efficacy Evaluable Population (EFF) includes all patients in the SAF with measurable disease at baseline per RECIST 1.1 who had at least one evaluable post-baseline tumor assessment unless discontinued due to clinical disease progression or death within 7 weeks of the first dose date.

The PK population (PK) includes patients who contributed at least 1 post-dose quantifiable PK sample.

9.1.2. Patient Disposition

The number of patients enrolled, 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 discontinued will be summarized according to the categories in the eCRF. The end of study status (alive, dead, withdrew consent or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

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

9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis; categorical variables include, gender, ECOG, geographical region, country, race, Child-Pugh classification, hepatitis virus, BCLC staging, metastatic site, and macrovascular invasion and/or extrahepatic spread status.

9.1.4. Prior and Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary drug codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical 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 taken within 30 days of the first dose of study drug that were stopped prior to study drug administration. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of Safety Follow-up visit). A listing of prior and concomitant medications will be included in the CSR for this protocol.

9.2. Efficacy Analyses

9.2.1. Primary Efficacy Analyses

Hypothesis testing of ORR per IRC in the SAF will be the primary efficacy analysis. Efficacy endpoints based on investigator-assessed tumor response will be presented as the secondary efficacy analyses.

The ORR of BGB-A317 per IRC is assumed as 15% in patients with previously treated unresectable HCC. The historical rate in a similar population is estimated as 7%. The null and alternative hypotheses are set as follows:

H0: ORR = 7%

Ha: ORR ≥ 15%

A binomial exact test will be performed for hypothesis testing. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that BGB-A317 monotherapy statistically significantly increases ORR compared with historical control. Therefore, the superiority of BGB-A317 monotherapy will be demonstrated. A two-sided binomial exact 95% CI of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, anticipated as no more than 6 months after the last subject received the first dose of study drug. In case of significant enrollment delay in the second line or third line (or more) population, a sub-population focused analysis may be performed once a given population has reached its enrollment target.

9.2.2. Secondary Efficacy Analyses

Other tumor assessment outcomes per IRC or investigator will be summarized as well as OS as secondary efficacy analysis.

The KM method will be used to estimate the key secondary endpoint DOR and corresponding quantiles (including the median), if estimable, in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method (Brookmeyer and Crowley, 1982).

The DOR censoring rule will follow the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (FDA, 2007). Censoring rules following the European Medicines

Agency Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA, 2012) will be used as a sensitivity analysis.

Other time to event variables (PFS and OS) will be similarly analyzed in the SAF using the KM method as described above. The KM estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis set who remain alive and progression-free at the specified time points (ie, 3 or 6 month), will be estimated using the KM method along with the corresponding 95% CI constructed using Greenwood's formula (Greenwood, 1926). The OS time point estimates will be calculated similarly.

Binomial exact 95% CI of DCR and CBR will be calculated in the SAF.

9.3. Safety Analyses

All patients who were exposed to BGB-A317 will be evaluated for safety.

9.3.1. Extent of Exposure

Extent of exposure to BGB-A317 will be summarized descriptively as the number of doses received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity (in mg/3 weeks), and relative dose intensity.

The number (percentage) of patients requiring drug discontinuation due to AEs will be summarized.

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 (v 18.1 or higher) lower level term, preferred term and primary system organ class (SOC).

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the date of first dose of study drug up to 30 days following study drug discontinuation (Safety Follow-up visit) or initiation of new anticancer therapy. Treatment-emergent AEs also include all irAEs (BGB-A317 only) and related serious AEs recorded up to 90 days after the last dose of BGB-A317 regardless of whether or not the patient starts a new anticancer therapy. Only those AEs that were treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE v4.03 within an SOC and preferred term, even if the patient experienced more than 1 TEAE within a specific SOC and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug. Treatment-related AEs include those events considered by the investigator to be definitely, possibly or probably related to study treatment or with missing assessment of the causal relationship. All SAEs, deaths, TEAEs ≥ Grade 3, irAEs, 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) values will be evaluated as appropriate. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE v4.03 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 will be summarized separately.

9.3.4. Vital Signs

Vital sign parameters and changes from baseline values will be listed by patient and visit.

9.3.5. Physical Examination

Physical examination results will be listed.

9.3.6. Ophthalmologic Examination

Ophthalmologic examination results will be listed by patient.

9.4. Pharmacokinetic Analysis

Pharmacokinetic samples will be collected in this study as outlined in Appendix 1, and only from patients receiving BGB-A317 at sites that are able to adequately perform PK sampling, handling, and processing procedures as outlined in the laboratory manual. BGB-A317 postdose and trough serum concentration data (C_{trough}) will be tabulated and summarized by visit/cycle at which these concentrations are collected. Descriptive statistics will include means, medians, ranges, and standard deviations, as appropriate.

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

9.5. Immunogenicity Analysis

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. Exploratory Analyses

The primary predictive biomarker analysis is based on a subset of the patients with both a valid PD-L1 expression and/or tumor-infiltrating lymphocytes (TILs) measurement and at least one disease assessment post-treatment. A supportive analysis is based on patients with a valid PD-L1 expression and/or TILs

measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response. Exploratory analyses of other candidate predictive biomarkers, including but not limited to gene expression profiling, will be conducted similarly.

9.7. Sample Size Consideration

The ORR per IRC is assumed as 15% in this trial. With 228 patients, the power is 0.97 to demonstrate that the ORR in patients with previously treated unresectable HCC is statistically higher than the historical rate of 7% (Bruix et al, 2017) in a binomial exact test. The 95% CI of an observed 15% ORR is (10.6%, 20.3%) when approximately 228 previously treated unresectable HCC patients are enrolled. Within 2nd line or 3rd line plus patients, the 95% CI of the same ORR is (8.6%, 23.5%) when n=100 in each population.

9.8. Interim Analyses

No interim analyses are planned.

10. STUDY COMMITTEES AND COMMUNICATION

10.1. Independent Review Committee

An IRC will be established to perform an independent review of all radiological images for the efficacy analysis, and to determine all instances of response and disease progression on the basis of the RECIST v1.1 criteria, in addition to the local investigator review of radiographs. The results from the investigator's review of radiographic images will be used to determine whether patients should be enrolled or should continue on study treatment. The tumor assessment by IRC will be used for the reporting of the study results.
All decisions made during the performance of the study will be on the basis of the local investigator's assessment of radiographic images, clinical status, and relevant examination of the patients. Sites will submit specific radiographic image files to the centralized data review facility during the study on an ongoing basis or at the sponsor's request. Detailed rules and guidelines for radiographic imaging and tumor assessments by IRC are outlined separately in the Imaging Manual and IRC Charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

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

11.1. Access to Information for Monitoring

In accordance with the International Conference 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 in the course of these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

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

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

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

12.2. Quality Assurance

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

12.3. Study Site Inspections

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

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

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records and returned or destroyed study product. Dispensation records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, 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 (see Pharmacy Manual). At the end of the study, following final 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 PATIENTS

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 IRB/IEC by the principal investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC.

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

13.2.1. Protocol Amendments

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

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

As discussed in Section 7.5, 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.

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 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 investigational new drug, and any other study information, remain the sole and exclusive property of sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

13.5. Financial Disclosure

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

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

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or delegated designee, who is included on Form FDA 1572 (or equivalent, such as a Statement of Investigator, as applicable for Non-US Investigators), must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

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

14.1.2. Data Management/Coding

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

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file 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) 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.

Electronic CRF 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.

Adverse events and concomitant diseases/medical history will be coded using MedDRA v 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary.

14.2. 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 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, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some 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.

14.3. 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.

14.4. 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 or stricter local criteria (International Committee of Medical Journal Editors, 2016).

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

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

14.5. 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
- Shipment of PK samples to assay laboratories

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

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

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for 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.

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

These restrictions do not apply to:

- Information 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 14.4

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

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Assessment	Screening[1]	Treatment Period				End of Treatment[2]	Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3 (Every 21 Days)			Cycle 4 and Additional Cycles (Every 21 Days)			
Days (window)	**-28 to -1**	**1 (± 3 days for C2D1 and C3D1)**	**8 (± 2 days)**	**15 (± 2 days)**	**1 (± 3 days)**	**0 to 7 Days**	**30 (± 7 days) after last dose**	**Every 3 months (± 14 days)**
Informed consent[1]	x							
Inclusion/exclusion criteria	x							
Demographic/Medical History/ Prior medications[5]	x							
Vital signs/Weight[6]	x	x			x	x	x	
Physical examination	x	x			x	x	x	
ECOG performance status	x	x			x	x	x	
12-lead ECG[7]	x	As clinically indicated						
Review adverse events[8, 24]	x	x	x[25]	x[25]	x	x	x	
Review concomitant medications	x	x	x[25]	x[25]	x	x	x	
Hematology[9]	x	x	x	x	x	x[2]	x	
Comprehensive serum chemistry panel[9]	x	x	x	x	x	x[2]	x	
Coagulation parameters[9, 10]	x	As clinically indicated				x[2]		
Urinalysis[9]	x	As clinically indicated				x[2]		
Pregnancy test[11]	x	x			x		x	
Thyroid function[12]	x				x		x	
Anti-BGB-A317 antibodies[13]		x			x		x	
Pharmacokinetics[14]		x			x		x	

Assessment	Screening[1]	Treatment Period				End of Treatment[2]	Safety Follow-up[3]	Survival Follow-up[4]
		Cycles 1 to 3 (Every 21 Days)			Cycle 4 and Additional Cycles (Every 21 Days)			
Days (window)	**-28 to -1**	**1 (± 3 days for C2D1 and C3D1)**	**8 (± 2 days)**	**15 (± 2 days)**	**1 (± 3 days)**	**0 to 7 Days**	**30 (± 7 days) after last dose**	**Every 3 months (± 14 days)**
Pulmonary function tests[15]	x							
Hepatitis B and C tests[16]	x	As clinically indicated						
Alpha fetoprotein	x	x			x	x		
Tumor imaging[17]	x	x[17]			x	x		
Bone scan[18]	x				x[18]			
Child Pugh classification[26]	x							
Study drug administration		x			x			
Archival tumor tissues[19]	x							
Fresh tumor tissues[20]	x							
EQ-5D-5L[21]	x	x			x	x		
EORTC QLQ-C30[21]	x	x			x	x		
EORTC QLQ-HCC18[21]	x	x			x	x		
Survival status								x
Optical coherence tomography (or equivalent diagnostic test) and visual acuity tests[22]	x				x	x[23]	x[23]	

Abbreviations: AE, adverse event; C1D1, Cycle 1 Day 1; CR, complete response; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-HCC18, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Hepatocellular Carcinoma 18 Questions; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EOT, end of treatment; EQ-5D-5L, 5-level version of European Quality of Life 5-Dimensional questionnaire; HBsAg, hepatitis B surface antigen; HBcAb, hepatitis B core antibody; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; PD, progressive disease; PD-L1, programmed cell death protein ligand-1; PK, pharmacokinetics; PR, partial response; TSH, thyroid stimulating hormone.

1. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (eg within 28 days prior to Cycle 1 Day 1). If laboratory tests at screening are not performed within 7 days prior to the administration of study drug(s) on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed prior to treatment authorization.
2. The End of Treatment (EOT) visit is defined as the day on which the investigator determines that BGB-A317 will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry, and alpha fetoprotein) are completed within 7 days before the EOT Visit, repeat tests are not required; coagulation and urinalysis should be conducted at the EOT visit only if clinically indicated. Tumor assessment does not need to be repeated at the EOT visit if the time interval from the last assessment is < 6 weeks.
3. The mandatory Safety Follow-Up visit should be conducted 30 days (±7 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related AE will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first. Follow-up for an irAE will occur until 90 days after treatment discontinuation regardless of whether or not the patient starts a new anticancer therapy.
4. Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 14 days) after the Safety Follow-up Visit until death, loss to follow-up, withdrawal of consent, or study termination by sponsor, whichever occurs first. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up. Information on irAEs will be collected up until 90 days after the last dose of BGB-A317 regardless of whether or not a patient starts a new anticancer therapy.
5. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Other concurrent conditions should be reported as well. Complete medication history for 30 days before the first dose (C1D1) of study medication needs to be reported.
6. Vital signs to include temperature, pulse, and blood pressure (see Section 7.4.1 for additional instructions).
7. Subsequent ECGs are required only for patients with clinically significant findings during screening.
8. Adverse experiences and laboratory safety measurements will be graded per NCI-CTCAE v 4.03. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness (see Section 8.4). After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After the first dose of study drug, all AEs and SAEs, regardless of their assessed relationship to study drug, are to be reported until either 30 days after the last dose of BGB-A317 or the initiation of new anticancer therapy, whichever occurs first. All irAEs will be reported for 90 days after the last dose of BGB A317, regardless of whether or not the patient starts a new anticancer therapy. The investigator should report any SAEs that are assessed as related to BGB-A317 treatment at any time after treatment discontinuation.
9. Local or central laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 4. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug on Cycle 1 Day 1, chemistry, hematology, and coagulation tests should be repeated and reviewed prior to treatment authorization. Hematology and serum chemistry (including liver function tests) specified in Appendix 4 will be performed weekly for the first 3 cycles and then at the beginning of subsequent cycles. These tests may be conducted in local laboratories. After Cycle 1, results are to be reviewed within 2 days before study drug administration. Coagulation and urinalysis are to be conducted during the treatment period only if clinically warranted. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
10. Includes International Normalized Ratio, Prothrombin Time, and Activated Partial Thromboplastin Time, analyzed by the local or central laboratory. Coagulation is to be conducted during the treatment period only if clinically indicated.

11. Only in women of childbearing potential. Patients must have a negative pregnancy test (serum or urine) within 7 days before the first investigational product administration. If the screening urine pregnancy test has not been done within 7 days of first dose, it would need to be repeated at Cycle 1 Day 1, prior to dosing. A urine pregnancy test should be performed at each subsequent visit. A blood test should be performed to confirm an equivocal or positive urine pregnancy test.
12. Analysis of free T3, free T4 and TSH will be performed by the local or central laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10 etc) and at the mandatory Safety Follow-Up Visit.
13. Blood used to test for anti-BGB-A317 antibodies should be collected within 60 minutes before beginning the Day 1 infusion of Cycles 1, 2, 5, 9, and 17 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.
14. Samples for PK analysis will be collected only at sites that are able to adequately follow the sampling, handling, and processing procedures described in the lab manual. Predose (within 60 minutes before starting infusion) are required to be collected on Day 1 of Cycles 1, 2, 5, 9. And 17. Two postdose samples (within 30 minutes after completing BGB-A317 infusion) are required to be collected on Day 1 of Cycles 1 and 5. An additional PK sample is required to be collected at the mandatory Safety Follow-Up Visit. Should a patient present with a ≥ Grade 3 irAE (refer to Section 8.7), additional blood PK samples will be taken to determine the serum concentration of BGB-A317. These tests are required when it is allowed by local regulations/IRBs/IECs.
15. 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. Results of pulmonary function testing should be reviewed prior to treatment authorization.
16. Testing will be performed by the local/central laboratory at screening and include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA). Patients who have detectable HBV DNA or HCV RNA at screening will perform the respective viral load test every 4 cycles (ie, Day 1 of Cycle 5, 9, 13, etc).
17. 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 study drug administration may be used for the purposes of screening., During the study tumor imaging will be performed approximately every 6 weeks (± 7 days) in the first 18 weeks and every 9 weeks (± 7 days) thereafter. The same imaging technique should be used in a patient throughout the study. After 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. Progressive disease suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later but not exceeding 6-8 weeks from the date of initial documentation of PD. 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, dies, 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. See Section 7.5 for detailed information regarding tumor evaluation.
18. Bone scans at baseline or subsequent visits will be performed only if clinically indicated.
19. An archival tumor sample (if available) is required to be collected for the purpose of biomarker analysis such as PD-L1 expression and gene expression profiling. Specific instructions for tissue collection and shipment are provided in the Lab Manual.

20. Collection of a fresh tumor biopsy at baseline will be optional for biomarker analysis, if accessible and appropriate. Please refer to Section 7.8 for biopsy requirements. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (eg, skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a core or excisional biopsy of the tumor (cytologic or fine-needle aspiration samples are not acceptable) should be obtained that has proper size for histological examination and biomarker analysis.
21. To be completed prior to any clinical activities during on-study site visits. These assessments will be completed at screening and/or baseline, then every other cycle (6 weeks) starting from Cycle 2 until Week 36 (Cycle 12), and subsequently every 12 weeks.
22. 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 first study drug administration may be used rather than repeating tests. Eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed at the Screening Visit. Patients will undergo repeat assessments approximately every 15 weeks (± 7 days).
23. The ophthalmologic assessments including eye exam, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) should only be performed once at either the EOT or during safety follow up, within 30 days of study treatment end.
24. Investigators should solicit patients regarding changes in vision, visual disturbance, or ocular inflammation at each scheduled study visit during BGB-A317 treatment. For any change in vision, referral to an appropriate specialist will be made for further management guidance.
25. Review of AEs and concomitant medications may be conducted by telephone on Days 8 and 15.
26. All Child-Pugh classification (Appendix 2) evaluations must be performed within 7 days of first study drug administration.

APPENDIX 2. CHILD-PUGH CLASSIFICATION SCORING SYSTEM

The information presented here has been obtained from the Washington University Medical Center, with sources as follows: Lucey et al, 1997; Pugh et al, 1973; Trey et al, 1966.

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 Prothrombin 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 by exchange blood transfusion. N Engl J Med. 1966;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 Transpl Surg. 1997;3(6):628-637.

Abbreviations: INR = International Normalized Ratio; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events, CPS = Cycles Per Second

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, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about 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 MD, Group Chair.	

APPENDIX 4. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Direct bilirubin Total bilirubin Blood urea nitrogen or urea Creatinine Glucose Lactate dehydrogenase Total protein Potassium Sodium Creatine kinase Creatine kinase-cardiac muscle isoenzyme (CK-MB)[2]	Hematocrit Hemoglobin Platelet count WBC count Neutrophil count Lymphocyte count	Prothrombin time Activated Partial Thromboplastin Time International Normalized Ratio	Glucose Protein Ketones Blood 24-hour protein[1] Random urine protein to creatinine ratio

Abbreviations: WBC, white blood cell.

Note: Additional laboratory assessments may be conducted if required for clinical management; relevant data from those assessments will be collected by the sponsor.

1. 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.
2. In the event CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from Eisenhauer et al, 2009.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

Measurable Disease

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

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

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

Nonmeasurable Disease

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

Bone lesions:

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

Cystic lesions:

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

Lesions with prior local treatment:

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

Target Lesions

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

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

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

Nontarget Lesions

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

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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

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

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

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

developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

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

RESPONSE CRITERIA

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure".

  When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of

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

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

Evaluation of Nontarget Lesions

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

- CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: the appearance of one or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- When the patient has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable

in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).

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

New Lesions

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

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

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

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of PD based on a new lesion.

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

Evaluation of Best Overall Response

The BOR 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 BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The BOR is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR). When SD is believed to be 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".

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 SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

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

Duration of Overall Response

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

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

Duration of Stable Disease

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

The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of patients achieving SD 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 SD.

Note: The duration of response and SD as well as the PFS 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 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

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

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

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

APPENDIX 7. 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 BGB-A317 and the adverse event?
- How did the patient respond to withdrawal of BGB-A317?
- Did the event recur when BGB-A317 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.

Immune-related Toxicity	Diagnostic Evaluation Guideline
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, Clostridium difficile toxin, cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye Disorders	If patients experience acute, new onset, or worsening eye inflammation, blurred vision or other visual disturbance refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if grade 3-4; every 2-3 days if grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging, eg, ultrasound scan for metastases or thromboembolism. Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status, and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

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

Treatment of Immune-related Adverse Events

- Immune-related AEs can escalate quickly; Study treatment interruption, close monitoring, timely diagnostic work-up and treatment intervention, as appropriate, with patients is required
- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice and contact the study medical monitor
- For some grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study medical monitor
- Steroid dosages in the table below are for oral or intravenous (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-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider Pneumocystis infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg,	Discontinue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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. Retreat 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 review.	Discontinue study treatment.
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs within 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if 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.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: · If on oral prednisolone change to pulsed IV methylprednisolone · If on IV add mycophenolate mofetil (MMF) 500-1000 mg twice a day · If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine > 1.5-3X baseline or > 1.5-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1**	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against	Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
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/worsen, 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 guideline, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as grade 3.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 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	Hold study treatment until improved to grade 0-1. Discontinue if any evidence of myocardial involvement

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
		improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	
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, chronic heart failure; CK, creatine kinase; CK-MB, creatine kinase-cardiac muscle isoenzyme; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 8. MANAGEMENT OF INFUSION-RELATED REACTIONS

Treatment modification guidelines for suspected infusion-related reactions due to BGB-A317 are summarized below.

NCI-CTCAE Grade	Treatment Modification for BGB-A317
Grade 1 or 2 Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease BGB-A317 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 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for $\leq$ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to at least grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 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 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 treatment. Hospitalization is recommended.

Abbreviations: IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSAID, nonsteroidal anti-inflammatory drug.

Once the BGB-A317 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 ($\geq$ Grade 2) on the slower infusion rate, infusion should be discontinued and the patient should be withdrawn from BGB-A317 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 antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (eg, diphenhydramine or equivalent) and an 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, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[1] and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

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

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

APPENDIX 10. GUIDANCE ON DEFINITION OF FIRST-LINE OR SECOND-LINE TREATMENT

Investigators enrolling patients in this study are provided the following guidance regarding the definition of prior therapy. Eligibility of patients who have received therapies not meeting the criteria outlined below should be discussed with the BeiGene medical monitor.

The following criteria define an acceptable course of first-line therapy:

- Oxaliplatin-based chemotherapy, sorafenib, lenvatinib, and other investigational agent with demonstrated efficacy in a Phase 3 clinical trial
- Prior sorafenib or lenvatinib for at least 28 days (not necessarily consecutive) and chemotherapy for at least 1 cycle before discontinuing the therapy due to radiographic or symptomatic progression or intolerance
- Progression on treatment was defined as radiographic progression (eg, RECIST v 1.1) or symptomatic progression defined as a decrease of ECOG performance status from 0 to 1 and/or development of symptomatic disease from asymptomatic disease
- Intolerance was defined as persistence of treatment-related AEs of at least grade 2, despite supportive therapy, and/or persistence/recurrence of AEs after dose interruption and reduction of sorafenib

The following criteria define an acceptable course of therapy in the second-line setting and beyond:

- Use of regorafenib, cabozantinib, other approved agents for the treatment of HCC, or other investigational agents
- Patients must have experienced said therapy for at least 28 days (not necessarily consecutive) before discontinuing the therapy due to radiographic or symptomatic progression or intolerance (as described above)
- Intolerance was defined as persistence of treatment-related AEs of at least grade 2, despite supportive therapy, and/or persistence/recurrence of AEs after dose interruption and reduction of said treatment

APPENDIX 11. BARCELONA CLINIC LIVER CANCER (BCLC) STAGING CLASSIFICATION

The Barcelona Clinic Liver Cancer (BCLC) system has been widely validated and is the most commonly used staging system for HCC. It determines cancer stage and patient prognosis based on tumor burden, severity of liver disease, and the patient's performance status.

The staging according to the BCLC classification assigns prognoses based on clinical and tumor parameters and is summarized as follows:

BCLC Stage[a, b]				
Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Single <2 cm Carcinoma in situ Child–Pugh A, ECOG 0	Single or 3 nodules <3 cm Child–Pugh A-B, ECOG 0	Multinodular, Child–Pugh A-B, ECOG 0	Portal invasion, Extrahepatic spread, Child–Pugh A-B, ECOG 1-2	Child–Pugh C ECOG 3-4

a. Bruix J, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;150:835-853.

b. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.