Clinical Study Protocol

Protocol Title:	**Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors**
Protocol No.:	**BGB-A317-102**
Date of Final Protocol:	**July 15, 2016, Version 1**
Date of Protocol Amendment:	**January 20, 2017, Version 2** **September 08, 2017, Version 3** **January 30, 2019, Version 4**
Study Phase:	**I/II**
Sponsor:	**BeiGene (Shanghai) Co., Ltd.** 4th Floor, Building D 780 Cailun Road China (Shanghai) Pilot-free Trade Zone Shanghai, China 201203
Medical Monitor:	[redacted] China
Principle Investigator:	[redacted]
Coordinating Investigator:	[redacted]
Coordinating Investigator:	[redacted]

If there are any discrepancies between the English and the Chinese version of the protocol, the Chinese version is the one to be used.

PROTOCOL APPROVAL SHEET

PROTOCOL TITLE: Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors

PROTOCOL NO: BGB-A317-102, Version 4, Dated 30 January 2019

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

_____ _____

[redacted]

Date

INVESTIGATOR SIGNATURE PAGE

Protocol Title: Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors

Protocol No.: BGB-A317-102

The protocol is a confidential document of BeiGene (Shanghai) Co., Ltd., and only disseminated under the premise of confidentiality. I confirm that I have read the protocol, understood the contents herein, and will carry out work in accordance with the protocol. In addition, I will carry out work according to the ethical principles in the Declaration of Helsinki, Good Clinical Practice and applicable laws and regulations. Signing the document means that I agree: without the prior written permission of BeiGene (Shanghai) Co., Ltd., I am prohibited to publicize or disclose non-public information herein.

Instructions for investigator: Please sign on the signature page and specify the date. Write your name in regular script, title and the name of the center to carry out the study. Please return a duplicate of the signed document to BeiGene.

I have read the entire protocol and agreed to carry out the study according to this protocol:

Investigator's Signature: _____

Investigator's Printed Name and title: _____

Date (dd mmm yyyy): _____

Name of the center in which the study will be conducted: _____

PROTOCOL AMENDMENT RATIONALE, VERSION 4.0

The main purpose of this protocol amendment is to define the end of the study and add an extension program to allow for maintenance of remaining ongoing patients. In addition, the assessment of adverse event causality has been changed to a 5-point scale, incorporating the note to file issued after the protocol amendment 3.0. Changes were made to the synopsis to match changes made in the protocol body.

In addition, the language and format of the protocol (including the protocol synopsis) are amended to improve the clarity and consistency throughout the document. This protocol amendment version number is updated to version 4.

Section	Key Changes	Rationale for Change
Title Page	• Update sponsor address • Update medical monitor, address	Consistency with protocols of other studies
Synopsis Section 3.3 Table 1 Table 4 Section 8.9	Revise exploratory endpoint for [redacted]	Clarify [redacted] investigation
Section 4.3	Clarify direction for dose delays	Incorporation of Note to File
Section 4.3 Section 10.7.1 Section 14	• Remove guidance from Section 4.3 on withholding treatment and discontinuing treatment that duplicates guidance in Appendix 3 • Add ASCO guidelines on management of immune-related adverse events • Add Brahmer 2018 reference	Consistency with Appendix 3, incorporate updated guidelines
Section 4.4 Table 1 Table 2 Table 3 Table 4	• Add section describing End of Treatment visit • Allowed for End of Treatment Visit to be used for Safety Follow-up Visit in some circumstances • Increase window to 7 days for routine laboratory tests to be usable for End of Treatment Visit • Increased Safety Follow-up Visit window to 30 ± 7 days after last dose	Consistency with protocols of other studies
Table 1 Table 4 Section 8.2 Appendix 4	Remove assessment of serum tumor markers	Will not be assessed

Section	Key Changes	Rationale for Change
Section 5.1 Appendix 5	• Add contraception guidelines • Add appendix on contraceptive guidelines	Consistency with protocols of other studies
Section 5.6	Clarify access for patients who wish to continue therapy beyond 2-year treatment period.	Increase patient access
Section 5.7	Provide for patients who choose to discontinue therapy once 2-year treatment period ends, but subsequently experience progressive disease and wish to reinitiate treatment.	Increase patient access
Section 5.7	Add End of Study definition	Clarify planned study end
Section 5.8	Specify that drug product will be provided to patients who wish to continue therapy beyond end of study	Increase patient access
Section 10.2.2 Section 10.6.1	Extend immune-related adverse event recording	Consistency with protocols of other studies
Section 10.3.3	Modify the assessment of AE causality back to 5 scales method as “definitely related” / “probably related” / “possibly related” / “possibly unrelated” and “unrelated”	Incorporate Note to File
Section 10.3.5	Clarify recording of laboratory test abnormalities as adverse events	Consistency with protocols of other studies
Section 10.5	Clarify definition of suspected unexpected serious adverse reaction	Consistency with protocols of other studies
Section 10.6.2.1 Table 7 Section 10.6.2.2 Section 10.6.2.3	Minor changes to reporting of serious adverse events	Consistency with protocols of other studies
Section 10.6.x	Remove sections on “Recording Diagnosis Versus Signs and Symptoms,” “Recording Adverse Events Occurring Secondary to Other Events,” and “Recording Poststudy Adverse Events”	Consistency with protocols of other studies

Section	Key Changes	Rationale for Change
Section 10.6.4	Remove direction to record persistent adverse events only once.	Consistency with CRF completion guidelines
Section 10.6.5 Section 10.6.6	Clarify reporting Disease Progression, Death	Consistency with protocols of other studies
Section 14	Update Investigator's Brochure to new version	Update references
Appendix 3 Appendix 4	• Add guidance for additional autoimmune toxicities • Add additional safety measures of myocarditis/myositis • Sorted tables	Consistency with protocols of other studies. Address reports of fatal immune checkpoint inhibitor-associated myocarditis

SYNOPSIS

Name of Sponsor:	**BeiGene (Shanghai) Co., Ltd.**	
Name of Finished Product:	**BGB-A317 Injection**	
Name of Active Ingredient:	**BGB-A317**	
Title of Study:	Phase I/II Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activities of Anti-PD-1 Monoclonal Antibody BGB-A317 in Chinese Patients with Advanced Solid Tumors	
Protocol No.:	**BGB-A317-102**	
Study centers:	Approximately 8 centers for Phase I. Approximately 20 centers for Phase II	
Study duration: Screening (up to 28 days), Treatment (up to 2 years of active therapy), Safety Follow-up (30 days) and Survival Follow-up.		**Phase:** I/II

Study Objectives:

Primary:

<u>Phase I</u>

<u>Dose Verification study</u>

- To assess the safety and tolerability of BGB-A317 in subjects with advanced solid tumors.
- To determine the maximum tolerated dose (MTD), if any, and/or the recommended Phase II dose (RP2D) for BGB-A317 in Chinese subjects

<u>Pharmacokinetics (PK) sub-study</u>

- To assess the PK of the products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP; FMP: Final Manufacturing Process) following the first dose of BGB-A317
  Notes: 500L-FMP indicates a final manufacturing process and scale of 500L; 2000L-FMP indicates a final manufacturing process and scale of 2000L.
- To assess the safety and tolerability of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP) in patients with advanced solid tumors

<u>Phase II</u>

- To assess the preliminary anti-tumor activity of BGB-A317.

Secondary:

Phase I

Dose Verification Study

- To characterize the pharmacokinetics of BGB-A317
- To assess the preliminary anti-tumor activity of BGB-A317
- To assess the host immunogenicity to BGB-A317

PK sub-study

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the multiple doses of BGB-A317
- To assess the host immunogenicity to BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP)
- To assess the preliminary anti-tumor activities of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP)

Phase II

- To further assess the safety and tolerability of BGB-A317
- To further assess the pharmacokinetic characteristics of BGB-A317
- To assess the host immunogenicity to BGB-A317

Exploratory Objective (Phase I & II)

- [redacted]

Study design	This is a multi-center, open-label, non-randomized Phase I/II clinical study, of which the Phase I PK sub-study is a parallel and multiple-dose study that is assessing PK of BGB-A317 derived from two manufacturing process and scales (500L-FMP and 2000L-FMP)
Planned number of subjects:	Approximately 288 subjects will be enrolled in the study. Of them, 68 subjects will be enrolled in the Phase I study (the first 20 subjects for dose verification study and the remaining 48 subjects for PK sub-study assessing the pharmacokinetics of the products derived from two manufacturing process [500L-FMP and 2000L-FMP]). The other 220 subjects will be enrolled in the Phase II study.
Study Population	

	Inclusion criteria: Subjects eligible for this study must meet all following criteria: 1. Voluntarily signed informed consent form for the study 2. Aged ⩾18 years on the day of signing informed consent 3. Subjects must have a histologically or cytologically confirmed advanced or metastatic tumor (unresectable), have had progression or intolerability since last standard anti-tumor treatment, or have no standard treatment or have refused standard therapy, as well as meet following requirements of tumor types in the corresponding stages: a) Phase I: Including but not limited to non-small cell lung cancer (NSCLC), melanoma, gastric cancer, esophageal carcinoma, ovarian cancer, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma (RCC) and triple negative breast cancer (TNBC) b) Phase II: • Arm 1 - melanoma, excluding uveal or ocular melanoma • Arm 2 - NSCLC (Program Death Ligand 1 [PD-L1]) positive) and Arm 3 - NSCLC (PD-L1 negative): i. PD-L1 detection must be confirmed prospectively at the central laboratory designated by the sponsor (refer to Section 8.9 for the definition of PD-L1 positive) ii. Subjects with known EGFR mutations (EGFR detection methods and results need to be approved by the study site) are excluded; subjects with non-squamous carcinoma of unknown EGFR mutations must be tested prospectively at the central laboratory designated by the sponsor, and subjects are excluded if tested positive iii. Subjects with known ALK gene translocation are excluded • Arm 4 - gastric cancer: gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma) • Arm 5 - esophageal carcinoma: esophageal squamous cell carcinoma • Arm 6 - RCC: RCC containing the component of clear cell • Arm 7 - urothelial carcinoma: locally advanced or metastatic urothelial transitional cell carcinoma (including renal pelvis, ureter, bladder and urethra) • Arm 8 - microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC): subjects with documented MSI-H or dMMR are

	eligible if tumor samples and blood samples are provided for retrospective confirmation at the central laboratory designated by the sponsor; subjects with unknown MSI or MMR mutations status must be tested prospectively before enrollment at the central laboratory designated by the sponsor (refer to Section 8.1 for detection methods) • Arm 9 - TNBC, HNSCC, small cell neuroendocrine carcinoma (SCNEC) or other tumors with known MSI-H or dMMR (subjects with documented MSI-H or dMMR are eligible if tumor samples and blood samples are provided for retrospective confirmation at the central laboratory designated by the sponsor, refer to Section 8.9 for detection methods) • Arm 10 - nasopharyngeal carcinoma (NPC): WHO type II-III (differentiated non-keratinizing type and undifferentiated non-keratinizing type) • Arm 11 - Child-pugh Class A hepatocellular carcinoma, excluding mixed hepatocellular and cholangiocellular carcinoma 4. Subjects must be able to provide archival tumor tissues (paraffin blocks or at least 10 unstained tumor specimen slides; subjects may be permitted to be enrolled on a case-by-case basis after discussion with the medical monitors from the sponsor if less than 10 unstained slides are provided), or newly obtained tumor tissue that has not been radiated, and relevant pathological reports. Refer to Section 8.9 for the requirements for tumor samples For subjects who have easily accessible tumor lesions and consent to biopsies, fresh baseline or paired tumor biopsies are strongly recommended for [redacted]. For **Arm 1 (melanoma)** in Phase II, tumor biopsies must be performed at baseline if feasible (biopsy is not required for subjects who provide archival tissue samples obtained within 12 weeks before treatment starts). Subjects may be permitted to be enrolled on a case-by-case basis after discussion with the medical monitors if biopsy specimens are not available 5. Subjects must have at least one measurable lesion as defined per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 6. Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 1$ 7. Life expectancy $\geqslant$ 12 weeks 8. Subject must have adequate organ function as indicated by the following laboratory values:

a) Absolute neutrophil count (ANC) $\geqslant$ 1.5 x 10^9/L
b) Platelets $\geqslant$ 75 x 10^9/L
c) Hemoglobin $\geqslant$ 90 g/L
d) Serum creatinine $\leqslant$ 1.5 X upper limit of normal (ULN)
e) Serum total bilirubin $\leqslant$ 1.5 X ULN (total bilirubin must be < 3 X ULN for subjects with Gilbert's syndrome)
f) International Normalized Ratio (INR) or Prothrombin Time (PT) $\leqslant$ 1.5 X ULN
g) Activated Partial Thromboplastin Time (aPTT) $\leqslant$ 1.5 X ULN
h) Aspartate transaminase (AST) and alanine aminotransferase (ALT) $\leqslant$ 2.5 X ULN, or AST and ALT $\leqslant$ 5 X ULN for subjects with liver metastases or hepatocellular carcinoma

9. Female subjects are eligible to participate in the study if they are:
   a) Non-childbearing potential (ie, physiologically incapable of becoming pregnant) who:
      - Has had hysterectomy
      - Has had bilateral oophorectomy
      - Has had bilateral tubal ligation or are post-menopausal (total cessation of menses for $\geqslant$ 1 year)
   b) Childbearing potential:
      - 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 dose of study drug
10. Non-sterile males 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

Exclusion criteria:

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

1. History of severe hypersensitivity reactions to other monoclonal antibodies
2. Prior malignancy active within the previous 2 years except for the tumor under investigation in this trial, cured or locally curable cancers, such as basal or squamous cell skin cancer,

	superficial bladder cancer or carcinoma in situ of the cervix or breast 3. Prior therapies targeting PD-1 or PD-L1 4. Active brain or leptomeningeal metastases. Subjects with brain metastases are permitted if they are asymptomatic, eg, diagnosed incidentally by brain imaging, or subjects with previously treated brain metastases that are asymptomatic at screening, radiographically stable and not requiring steroid medications for at least 4 weeks prior to the first administration of study treatment 5. Subjects with active autoimmune diseases or history of autoimmune diseases or immunodeficiency that may relapse should be excluded. Subjects with following diseases are allowed to be enrolled for further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or alopecia), or diseases not expected to recur in the absence of external triggering factors 6. Subjects should be excluded if they have a condition requiring systemic treatment with either corticosteroids (prednisone > 10 mg/day or equivalents) or other immunosuppressive medications within 14 days of study drug administration *Note:* Adrenal replacement doses of prednisone ⩽ 10 mg/day or equivalents are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted 7. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc 8. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc. (Antiviral therapy is permitted for subjects with hepatocellular carcinoma.) 9. With uncontrollable pleural effusion, pericardial effusion or ascites requiring repeated drainage 10. Significant cardiovascular diseases, such as heart failure of New York Heart Association cardiac disease Class II or

	greater, myocardial infarction within the previous 3 months, unstable arrhythmias or unstable angina Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate 11. History of alcohol or drug abuse or dependence 12. Known history of Human Immunodeficiency Virus (HIV) 13. Subjects with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA ⩾ 500 IU/mL (2500 copies/mL), or active hepatitis C should be excluded. Subjects with inactive hepatitis B surface antigen (HBsAg) carriers, active HBV infection with sustained viral suppression (HBV DNA < 500 IU/mL [2500 copies/mL]), and subjects whose hepatitis C has been cured can be enrolled 14. Underlying medical conditions that, in the investigator's opinion, will make an administration of study treatment hazardous or obscure the interpretation of toxicity determination or adverse events; or insufficient compliance during the study according to investigator's judgment 15. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies (including Chinese herbal medicine and Chinese patent medicines) used to control cancer must have been completed at least 2 weeks before the 1st study drug administration, and all adverse events have returned to either baseline or grade 0~1 according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (except for alopecia) 16. Use of any live or attenuated vaccines within 4 weeks (28 days) prior to initiation of study therapy 17. Major surgical procedure (Grade 3 or 4) within the past 4 weeks (28 days) prior to study drug administration 18. Prior allogeneic or solid organ transplantation
Investigational Drug, dose and mode of administration:	**Investigational Drug:** BGB-A317, 10 mL/vial, 10 mg/mL, intravenous infusion (IV) **Phase I (dose verification study):** Dose level: BGB-A317 200 mg Dosing frequency: once every 3 weeks (Q3W)

	The proposed dose level can be further adjusted according to the safety, tolerability and effectiveness observed in the dose verification study, and other doses may be added. **Phase I (PK sub-study):** Dose level: BGB-A317 200 mg Dosing frequency: Dosing on Day 1 with interval of 4 weeks for Cycle 1, Q3W for cycles thereafter **Phase II (indication expansion study):** Dose level and dosing frequency are used based on RP2D validated in Phase I dose verification study

Research method:

This study is a dose-verification, pharmacokinetic evaluation of the products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) and indication-expansion clinical study of monoclonal antibody BGB-A317 in Chinese subjects with advanced solid tumors, aiming at exploring the safety, tolerability, pharmacokinetics and preliminary efficacy of BGB-A317. This study is carried out on the basis of a Phase IA multi-dose and dose-escalation study in Australia. According to the preliminary results of the Phase IA clinical study in Australia, 0.5, 2, 5 and 10 mg/kg, once every two weeks (Q2W) are all tolerable doses. In addition, 2 and 5 mg/kg, Q3W have also been confirmed as tolerable doses.

This study can be divided into 2 parts. Phase I is a study of dose verification and pharmacokinetic evaluation of the products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) and Phase II is an indication expansion study. All subjects will receive BGB-A317 until they have no evidence of continued clinical benefits, unacceptable toxicity, or withdrawal of informed consent in the opinion of the investigator.

Phase I: It is a multicenter and open-label study.

Dose Verification Study (using BGB-A317 produced by 500L-OMP, OMP=Original Manufacturing Process)

3-6 subjects will be enrolled firstly to assess dose-limiting toxicity (DLT).

- If none of the 3-6 subjects experiences a DLT at the starting dose, enrollment will be continued until approximately 20 subjects in total are enrolled
- Three (3) additional subjects will be enrolled if a DLT is observed in one (1) of three (3) subjects; two (2) additional subjects will be enrolled if a DLT is observed in one (1) of four (4) subjects; and one (1) additional subject will be enrolled if a DLT is observed in one (1) of five (5) subjects. No additional subjects will be enrolled if a DLT is observed in one (1) of six (6) subjects
- If 2 or more subjects experience DLT in 3-6 subjects, such dose level will be considered as exceeding the MTD. All investigators will be informed of such dose level

DLT will be assessed among evaluable subjects within Cycle 1 (1-21 days). An evaluable subject is defined as the individual who has received at least 80% of the dose and completed all safety assessments required in Cycle 1, or any subject who has experienced DLT in Cycle 1.

A Safety Monitoring Committee (SMC) will be established by the sponsor and investigators. SMC will recommend RP2D based on the safety and tolerability of BGB-A317, and decide whether or not to add unscheduled doses for trial.

Dose level

According to the safety results of the dose-escalation trial on BGB-A317 conducted in Australia, this study will assess the safety and pharmacokinetic characteristics of flat dose 200 mg Q3W in Chinese patients with advanced malignant solid tumors, and other doses may be further explored based on the safety result and necessity.

Among the 3-6 subjects in the 200 mg Q3W cohort, if 2 or more subjects experience DLT within Cycle 1, such starting dose will be considered as exceeding the MTD, and a lower dose, such as 100 mg Q3W, will be assessed in 3-6 subjects.

If dose 200 mg Q3W passes the DLT assessment, the cohort at such dose level can be expanded to about 20 subjects to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamic characteristics of BGB-A317. In order to continuously monitor safety, when the cohort has been expanded to 10 subjects and $\geqslant$33% of them have experienced DLT within 21 days in Cycle 1, enrollment will be suspended, and an SMC meeting will be immediately held to discuss and determine whether such dose is safe.

Dose-limiting toxicity (DLT)

All toxicities or adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the investigator as possibly, probably or definitely related to study drug administration:

Non-hematologic toxicities:

1. Grade 4 or above toxicity

2. Grade 3 toxicity (regardless of duration), except for laboratory abnormalities, diarrhea, nausea, vomiting and asymptomatic biochemical abnormalities that is resolved to Grade 2 or lesser severity within 3 days after best supportive care

3. Grade 3 adverse event of tumor flare reaction (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) lasting >7 days

4. Grade 3 or above immune-related adverse events (irAE)

Hematologic toxicities:

1. Grade 4 neutropenia lasting >7 days

2. Febrile neutropenia (defined as absolute neutrophil count [ANC] $\leqslant$1000/mm^3 with a single temperature of 38.3^{o}C or a sustained temperature of 38^{o}C for >1 hour)

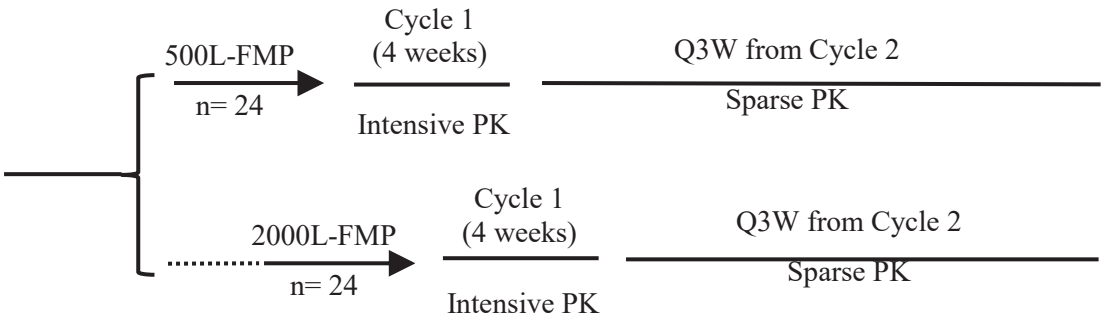
3. Grade 3 neutropenia with infection
4. Grade 3 thrombocytopenia with bleeding
5. Grade 4 thrombocytopenia
6. Grade 4 anemia (life-threatening)

And any grade of toxicity per the judgment of the investigator and sponsor requires premature discontinuation of the subject from the study.

Subjects who received <80% of the BGB-A317 infusion within Cycle 1 (eg, infusion-related reaction-caused infusion discontinuation) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

PK sub-study: It is a parallel and multiple doses study, which analyzes the PK and safety of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP). DLT and RP2D of all subjects are not assessed.

Total 48 subjects (24 per arm) are planned to be enrolled to receive treatment of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP). Cycle 1 lasts for 28 days, and Cycle 2 and those thereafter last for 21 days. If there is any drop-out before the complete of the first treatment cycle (28 days) of intensive PK, additional subjects will be enrolled until for each arm there are total 24 subjects complete the first treatment cycle. Schematic of the trial design is shown as below:



Abbreviation: FMP = Final Manufacturing Process; PK = pharmacokinetics; Q3W = once every three weeks

Phase II (indication expansion): To further assess the efficacy of BGB-A317 in Chinese patients with malignant solid tumors, once 200 mg Q3W has been confirmed as a tolerable dose in Chinese population and determined as RP2D, an indication-expansion study will be carried out among the following 11 groups of indications. Because of the changes of the manufacturing processes and scales during study, BGB-A317 of two manufacturing processes and scales (500L-OMP and 2000L-FMP) will be used for this Phase II study.

Arm 1: Melanoma

Arm 2: Non-small cell lung cancer (PD-L1 positive)

Arm 3: Non-small cell lung cancer (PD-L1 negative)

Arm 4: Gastric cancer

Arm 5: Esophageal cancer

Arm 6: Renal cell carcinoma

Arm 7: Urothelial carcinoma

Arm 8: MSI-H or dMMR colorectal cancer (CRC)

Arm 9: Triple negative breast cancer (TNBC), head and neck squamous cell carcinoma (HNSCC), small cell neuroendocrine carcinoma, or other tumors with MSI-H or dMMR

Arm 10: Nasopharyngeal carcinoma (NPC)

Arm 11: Hepatocellular carcinoma (HCC)

In the indication-extension study, about 20 subjects will be enrolled into each arm. For tumors that are difficult to enroll sufficient subjects, the sponsor may adopt premature termination of further subject enrollment in this arm. To fully assess the safety of BGB-A317, the contract research organization (CRO) and medical monitors from the sponsor will regularly review the safety data, and if necessary, will convene a temporary SMC meeting.

If subjects with a certain kind of tumor experience significant toxicities in the indication expansion study, the investigator and the sponsor will discuss and decide whether to conduct an independent study or to terminate the study in such tumors. Paraffin-embedded tumor tissue will be collected for purpose of [redacted]. However, if there is clinically appropriate biopsy lesion (biopsy is a must in specific cancer types in Phase II), a fresh tumor biopsy at baseline is strongly recommended. For these subjects, if possible, a biopsy for potential [redacted] after two cycles of treatment is strongly recommended. A written informed consent form (ICF) is required for fresh tumor biopsies.

Subjects will be monitored for safety, anti-BGB-A317 antibodies and efficacy throughout the study. Radiological assessment of tumor-response status should be performed approximately every 9 weeks in the first year, then every 12 weeks thereafter.

Tumor response will be assessed by investigators based on RECIST Version 1.1. For immune therapies such as that mediated by BGB-A317, pseudo-progression 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 progressive disease (PD) suspected by the investigator as pseudo-progression, the following criteria must be met in order to treat patients continuously until PD is confirmed by repeated imaging at least 4 weeks later or at the next scheduled imaging time point, but not exceeding 12 weeks from the date of initial documentation of PD: a. Absence of clinical symptoms and signs of disease progression (including clinically significant worsening laboratory values). b. Stable ECOG performance status. c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg cord compression) that necessitates urgent alternative medical intervention.

Criteria for evaluation:

Primary Endpoints:

Phase I

Dose Verification Study

- Safety and tolerability of BGB-A317: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events (SAEs) per NCI-CTCAE Version 4.03, physical examination, electrocardiograms and laboratory assessments
- The MTD (if any) and/or RP2D (s) for BGB-A317 will be determined based on safety, tolerability, pharmacokinetics, preliminary efficacy, and other available data

Pharmacokinetics (PK) sub-study

- PK: Single-dose pharmacokinetic parameters (maximum observed plasma concentration [C_{max}], and area under the plasma concentration and time curve [AUC_{last} and AUC_{inf}]) will be assessed to evaluate the PK characteristics of BGB-A317 derived from both manufacturing processes and scales
- Safety: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events per the NCI-CTCAE Version 4.03, physical examination, electrocardiograms, laboratory measurements

Phase II

- The objective response rate (ORR) in different tumor types will be determined by the investigator based on RECIST Version 1.1

Secondary Endpoints:

Phase I

Dose Verification Study

- Evaluations of Pharmacokinetics: include but not limited to $AUC_{0\text{-}21\ day}$, C_{max} and time to maximum observed plasma concentration (T_{max}), minimum observed plasma concentration (C_{trough}), $t_{1/2}$, clearance (Cl) and volume of distribution during terminal phase (V_z)
- Efficacy evaluations: ORR, complete response (CR) rate, partial response (PR) rate, stable disease (SD) rate, progression-free survival (PFS), duration of response (DOR), and duration of SD will be determined by investigator based on RECIST Version 1.1; overall survival (OS) will be evaluated
- Anti-BGB-A317 antibodies: immunogenic responses to BGB-A317 will be assessed by monitoring the occurrence of anti-drug antibody (ADA)

Pharmacokinetics sub-study

- PK: Steady-state pharmacokinetic parameters (include but not limit to C_{trough}) will be assessed for both manufacturing processes and scales following the multiple doses of BGB-A317 to evaluate the PK characteristics at steady state
- Immunogenicity: Immunogenic responses to BGB-A317 of both manufacturing processes and scales will be assessed to evaluate the comparability of the occurrence of anti-drug antibody
- Efficacy evaluations: ORR, Complete Response rate, Partial Response (PR) rate, SD rate, PFS, and DOR and duration of SD will be determined by investigator based on RECIST Version 1.1; OS will be evaluated

Phase II

- Evaluations of Efficacy: Complete Response rate, PR rate, SD rate, PFS, DOR, duration of SD, disease control rate (DCR) and clinical benefit rate will be determined by investigator based on RECIST Version 1.1; OS will be evaluated
- Safety and tolerability of BGB-A317: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events and serious adverse events per NCI-CTCAE Version 4.03, physical examination, electrocardiograms and laboratory assessments
- Evaluations of Pharmacokinetics: including but not limited to C_{trough}
- Anti-BGB-A317 antibodies: immunogenic responses to BGB-A317 will be assessed by monitoring the occurrence of anti-drug antibody (ADA)

Exploratory Endpoints:

[redacted]

Statistical methods:

Phase I Dose verification study: The sample size in the dose-verification study in Phase I depends on the number of dose levels to be assessed and the occurrence of DLT in each cohort. The necessity of assessing additional cohorts and the corresponding sample size will be determined by the safety of the dose to be investigated. Approximately 20 subjects will be enrolled.

Phase I PK sub-study: Total 48 subjects (receiving BGB-A317 either from 500L-FMP or from 2000L-FMP, respectively; 24 per arm) are planned to be enrolled in the PK sub-study. If there is any drop-out before the complete of the first treatment cycle (28 days) of intensive PK, additional subjects will be enrolled until for each arm there are total 24 subjects complete the first treatment cycle. Under the assumption of 30% variability (coefficient of variation [CV], from Study BGB-A317_001 PK data), this sample size will provide approximately 75 - 82% power to reject the null hypothesis to demonstrate that the population means of the 2 manufacturing processes and scales are equivalent. The power will be increased to 89% - 95% provided that the CV = 24% (from recent Study BGB-A317-102 PK data). The sample size calculation is only to provide a general guidance to enroll enough number of subjects in the descriptive PK analysis, no formal hypothesis testing of PK equivalence will be conducted.

Approximately 220 subjects are expected to be enrolled in the indication expansion stage in Phase II in order to analyze preliminary efficacy for BGB-A317 monotherapy. The statistical basis for the number of subjects enrolled into each cohort in Phase II will be illustrated in the Statistical Plan.

Data will be listed and summarized according to the sponsor-approved reporting standards, where applicable.

All subjects who have received (or about to receive) BGB-A317 will be included in the safety-analysis set. All subjects with valid BGB-A317 PK parameters after treatment will be included in the PK-analysis set. For other parameters, all evaluable data will be included in the summaries.

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

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration and time curve
BGB-A317	Code name for Monoclonal Antibody BGB-A317
CBC	Complete blood count
CBR	Clinical benefit rate
Cl	Clearance
C_{max}	Maximum observed plasma concentration
CR	Complete response
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum observed plasma concentration
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FMP	Final manufacturing process
GCP	Good Clinical Practices
GMP	Good Manufacture Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Independent Ethics Committee
IgG	Immunoglobulin G, such as IgG1, IgG2, IgG3 and IgG4; other types of immunoglobulins include IgM, IgD and etc.
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
MMR	Mismatch repair
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OMP	Original Manufacturing Process
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Program Death Ligand-1
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin Time
Q2W	Once every two weeks
Q3W	Once every three weeks
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
$t_{1/2}$	Half-life
T_{max}	Time to maximum observed plasma concentration
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Background and Pharmacology

Immune check point-inhibitory receptor, programmed cell death-1 (PD-1) is mainly expressed in activated T-cells including CD8+ cytotoxic T-lymphocytes and CD4+ T-helper lymphocytes (McDermott DF, 2013). It is believed that PD-1 plays an important role in immune modulation of tumor progression by regulating the key inhibitory signaling in the T-cells when engaged by its ligands. The PD-1 signaling cascade reaction negatively regulates T-cell receptor (TCR) and attenuates T-cell proliferation and functional activities, leading to T-cell exhaustion. PD-1 expression is markedly up-regulated in tumor-infiltrating lymphocytes, while the expression of PD-1 ligand, PD-L1, is significantly increased in tumor cells and tumor-associated immune cells in the presence of stimulating cytokines such as interferon (IFN)-γ and IFN-α in the tumor microenvironment (Riley JL, 2009). Furthermore, the increased PD-1 expression in tumor-infiltrating lymphocytes and/or PD-L1 expression in tumor and tumor-associated stromal cells is observed in many types of solid human tumors, including, but not limited to, melanoma, squamous cell carcinoma, uveal melanoma, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), triple-negative breast cancer, renal cell carcinoma (RCC), bladder cancer, and ovarian cancer (Ghebeh H, 2006; Hamanishi J, 2007; Hino R, 2010; Jie HB, 2013; Konishi J, 2004; Thompson RH, 2007; Thompson RH, 2004; Tsushima F, 2006). These evidences provided the basis for use of antagonists of PD-1 as cancer immunotherapeutic agents.

Recent clinical trials have demonstrated significant efficacy for anti-PD-1 monoclonal antibodies such as nivolumab and pembrolizumab in advanced melanoma, NSCLC and RCC. These antibodies were well tolerated without demonstrating dose-limiting toxicity (DLT) when patients were dosed up to 10 mg/kg intravenously, once every two weeks (Q2W) or once every three weeks (Q3W). The first-in-human phase I trial on nivolumab (a fully human anti–PD-1 immunoglobulin G4 [IgG4] antibody) evaluated its safety profile at increasing doses of 0.3, 1, 3 and 10 mg/kg given intravenously (IV) Q2W in 39 patients with advanced melanoma, colorectal cancer (CRC), castration resistant prostate cancer (CRPC), NSCLC, or RCC (Brahmer JR, 2010; Topalian SL, 2012). The FIH Phase I study on pembrolizumab (a humanized anti–PD-1 IgG4 antibody) evaluated its safety at 1 to 10 mg/kg IV at 4 week interval followed by bi-weekly doses in cohorts of three to six patients with various advanced solid tumors (Hamid O, 2013). The most common adverse events (AEs) were grade 1/2, including arthralgia, cough, diarrhea, fatigue, fever, nausea, pruritus, and rash. However, grade 3/4 treatment-related AEs occurred in 15% of patients and there were three deaths in the nivolumab study, all attributed to pulmonary toxicity. Grade 3/4 AEs were also reported in the pembrolizumab studies and one patient died of myocardial infarction while being treated for pneumonitis/pneumonia. Drug-related AEs of special interest (AEs with potentially immune-related etiology) included vitiligo, pneumonitis, hepatitis, colitis, thyroiditis, and hypophysitis.

Based on the overwhelming positive results that pembrolizumab and nivolumab demonstrated in their pivotal studies, US Food and Drug Administration (FDA) approved these two drugs for the treatment of metastatic melanoma in 2nd or 3rd line. In the nivolumab pivotal study, the cohort of 120 patients treated at 3 mg/kg Q2W exhibited an overall response rate (ORR) of 32% with 4 complete responses (CRs) and 34 partial responses (PRs). Thirteen patients have objective responses lasting 6 months or longer (FDA News Release, 2 Dec. 2014). In the pivotal study on pembrolizumab, 173 patients were treated with pembrolizumab at either 2 or 10 mg/kg dose, approximately 24% patients demonstrated tumors shrinkage (2 mg/kg regimen) (FDA News Release, 4 Sept. 2014).

Interestingly, melanoma patients who became resistant to ipilumumab treatment were still sensitive to pembrolizumab. The ORRs of ipilumumab-naïve and ipilumumab-resistant are 40% and 28%, respectively.

Anti-PD-1 antibody treatment not only generated higher response rate, but also prolonged overall survival (OS). In a cohort of 107 patients treated with nivolumab, 1 and 2 years OSs were 63% and 48%, respectively, with median OS at 17.3 months. Similarly, in a cohort of 411 patients treated with pembrolizumab, 1-year OS was 69% and 18-month OS was 62%, respectively (Weber JS, 2014ASCO).

In addition to melanoma, anti-PD-1 antibodies were also reported to be efficacious in other cancer types including NSCLC, RCC and HNSCC. In the NSCLC study, 129 patients were treated with nivolumab in 2nd, 3rd or 4th line, one-year or two-year survival rate were 42% and 24%, respectively, with median OS of 9.9 months. Retrospective analysis indicated both patients with K-Ras and EGFR mutations responded to the immunotherapy (BMS Press Release, 25 Oct. 2014).

Recent exploratory studies suggested that combinatory immunotherapies with anti-PD-1 antibody may provide more benefits to cancer patients. In one study in patients with metastatic melanoma, nivolumab in combination with ipilumumab generated remarkable ORR with two-year OS rate at more than 80%. Patients with wild type or mutant BRAF, with or without PD-L1 expression, all responded well to the combination treatment (Sznol M, 2014; Wolchok JD, 2013). Of note, the immune-related adverse events (irAEs) also increased significantly in the combination treatment.

BGB-A317 is a humanized IgG4 variant monoclonal antibody against PD-1. It is being developed for the treatment of human malignancies. BGB-A317 was manufactured under Good Manufacture Practice (GMP) quality control systems. The clinical trial drug product is formulated in an aqueous buffer with pH 6.5 and isotonic osmolarity. The suggested administration route is IV infusion after the appropriate dilution in 0.9% sodium chloride solution.

BGB-A317 binds to the extracellular domain of human PD-1 with high specificity and affinity (K_D = 0.15 nM) as demonstrated by receptor binding assays based on surface plasmon resonance. It competitively blocks the binding of both PD-L1 and Program Death Ligand L2 (PD-L2), inhibiting PD-1 mediated negative signaling in T-cells. In *in vitro* cell-based assays, the humanized antibody

consistently and dose-dependently enhanced the functional activity of human T-cells and pre-activated, primary peripheral blood mononuclear cells. In addition, BGB-A317 demonstrated anti-tumor activity in several human cancer allogeneic xenograft models, including A431 human epidermoid carcinoma, BCCO-028 colon cancer, and BCLU-054 NSCLC models. In these studies, peripheral blood mononuclear cells were co-injected with the human cancer cells (A431) or the tumor fragments (BCCO-028 and BCLU-054) into the immunocompromised mice.

The IgG4 variant antibody has very low binding affinity to Fc-gamma receptor III (FcγRIII) and Complement 1 q by *in vitro* assays, suggesting a low or no antibody dependent cellular cytotoxicity and complement dependent cytotoxicity effect in humans. Unlike natural IgG4 antibody, BGB-A317 has no observable Fragment antigen-binding (Fab)-Arm Exchange activity by the *in vitro* assay, predicting the antibody would be stable *in vivo*, unlikely forming bispecific antibody.

BGB-A317 binds to the cynomolgus monkey and human PD-1 with similar affinity, but does not bind to mouse PD-1 due to the significant sequence divergence from human and monkey PD-1. Therefore, cynomolgus monkeys were considered to be the relevant species for nonclinical safety evaluation.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of BGB-A317.

1.2 Pharmacokinetics and Absorption, Distribution, Metabolism, and Excretion

A pharmacokinetic study of BGB-A317 was conducted in monkeys at single doses of 3, 10, or 30 mg/kg or at repeat dose of 10 mg/kg weekly for 5 doses via IV infusion. The systemic exposure appeared to increase dose-proportionally without gender difference or accumulation. After single dose administration of 3, 10, or 30 mg/kg, the half-life ($t_{1/2}$) ranged from 74 to 183 hours; maximum observed plasma concentration (C_{max}) ranged from 90 to 999 µg/mL, and area under the plasma concentration and time curve $(AUC)_{0\text{-}1008h}$ ranged from 12,322 to 163,755 h × µg/mL; volume of distribution (V_d) was low, ranged from 22 to 52 mL/kg.

A pharmacokinetic bridging study for BGB-A317 manufactured from BI and JHL was conducted in monkeys at a single dose of 10 mg/kg via IV infusion. No marked differences on $t_{1/2}$, C_{max}, AUC, V_d, clearance (CL) and mean residence time were noted between the two batches.

The $t_{1/2}$ of BGB-A317 in monkeys supported once biweekly dosing in the repeat-dose toxicology study with adequate systemic exposure to support toxicology evaluation of BGB-A317. Based on pharmacokinetics (PK) results in monkeys, the V_d of BGB-A317 in humans is expected to be similar to that in monkeys. The $t_{1/2}$ of BGB-A317 in humans is expected to be 10-20 days depending on the actual dose levels, which allows multiple-dose treatment of BGB-A317 for humans with a dosing interval of 14 or 21 days to provide the target systemic exposure at the projected therapeutic dose of 0.5 to 10 mg/kg without excessive drug accumulation.

Refer to the IB for more detailed information on the pharmacokinetics properties of BGB-A317.

1.3 Toxicology

The toxicity and safety profile of BGB-A317 was elaborated 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.

No apparent toxicity was noted in both mice and monkeys following a single dose up to 100 mg/kg and in monkeys following a repeat dose up to 30 mg/kg biweekly for 13 weeks. The toxicokinetics profile was characterized in monkey studies and the systemic exposure appeared to be dose proportional without gender difference or accumulation over the dosing period. No apparent immunotoxicity was observed as no apparent changes in clinical pathology or histopathology were noted in these studies. The immunogenicity with positive anti-drug antibody (ADA) against BGB-A317 was noted in the single dose monkey study with one of two monkeys in each of three dose groups and in the repeat dose study with 8/12, 6/12, and 5/12 of animals at doses of 3, 10, and 30 mg/kg, respectively. The ADA against BGB-A317 was demonstrated to have neutralization function in a cell-based assay and it appeared to have some impact on the systemic exposure over the dosing period at 3 mg/kg, but little at 10 and 30 mg/kg.

The tissue cross reactivity of BGB-A317 was evaluated in normal human and cynomolgus monkey frozen tissues using immunohistochemistry method, with appropriate positive and negative controls. Under the study condition, no specific tissue cross reactivity with BGB-A317 was noted in both human and cynomolgus monkey tissues. Neither hemolytic effects induced by BGB-A317 in the rabbit blood cells nor increase of the cytokine release from human whole blood cells after treatment with BGB-A317 was observed in *in vitro* evaluations.

Overall, no apparent toxicity was noted in mice and monkey toxicity studies. No tissue cross reactivity was found in both human and monkey tissues, nor effect on cytokine release was observed in human whole blood assay. 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 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.

Refer to the BGB-A317 IB for more detailed information on the toxicology of BGB-A317.

1.4 Clinical Study

The first human clinical study of BGB-A317 was conducted in Australia in June 2015. It is an open-label, multi-dose Phase I trial including stages of dose escalation, schedule expansion, fixed-dose exploration and indication expansion, mainly aiming at exploring the safety, tolerability, pharmacokinetic characteristics and preliminary anti-tumor efficacy of BGB-A317 in patients with advanced tumors.

As of 29 March 2016, a total of 100 subjects were enrolled. Among them, 22 were enrolled for the dose-escalation stage, including 3 subjects for 0.5 mg/kg Q2W, 6 subjects for 2 mg/kg Q2W, 6 subjects for 5 mg/kg Q2W and 7 subjects for 10 mg/kg Q2W; 78 subjects were enrolled for the schedule expansion stage, including 20 subjects for 2 mg/kg Q2W, 19 subjects for 2 mg/kg Q3W, 20 subjects for 5 mg/kg Q2W, and 19 subjects for 5 mg/kg Q3W.

Within the dose range of 0.5 mg/kg Q2W to 10 mg/kg Q2W, BGB-A317 has demonstrated favorable safety and tolerability in the treatment of patients with solid tumors in Australia. During the 28-day DLT observation period, only 1 case of grade 3 colitis was reported in the 5 mg/kg Q2W dose-escalation cohort, which was determined as DLT (1/6). No DLT occurred in other dose escalation cohorts, and maximum tolerated dose (MTD) was not reached. Preliminary safety analysis showed that the most common treatment-emergent adverse events (AE) (≥10%) included fatigue (31%), diarrhea (21%), nausea (20%), constipation (16%), abdominal pain (14%), pruritus (13%), rash (12%), loss of appetite (12%), back pain (12%) and vomiting (10%). Immune-mediated adverse events were reported among 10 subjects, including colitis (one grade 3, two grade 2), diabetes mellitus (one grade 3, one grade 2), alanine aminotransferase (ALT) increase (one grade 3), diarrhea (one grade 2), worsening liver functions (one grade 2), hypothyroidism (one grade 1) and onychoclasis (one grade 1). As of 29 March 2016, 9 drug-related serious adverse events (SAE) were reported, including one grade 2 colitis in the 2 mg/kg Q2W dose escalation cohort (n=6), one grade 3 colitis in the 5 mg/kg Q2W dose escalation cohort (n=6), one grade 2 colitis and one grade 2 infusion-related reactions in the 5 mg/kg Q2W schedule expansion cohort (n=20), one grade 3 diabetic ketoacidosis, one grade 3 diabetes mellitus, one grade 3 hypotension and one grade 2 diarrhea in the 2 mg/kg Q2W schedule expansion cohort (n=20), and one grade 3 hypotension in the 5 mg/kg Q3W schedule expansion cohort (n=19). Other grade 3/4 adverse events considered as treatment-related by the investigator included one grade 3 ALT increase in the 2 mg/kg Q2W dose escalation cohort (n=6), one grade 3 hyperglycemia in the 2 mg/kg Q2W schedule expansion cohort (n=20), one grade 3 back pain and one grade 3 fatigue in the 5 mg/kg Q2W schedule expansion cohort (n=20), and one grade 3 fatigue and one grade 3 hyperglycemia in the 5 mg/kg Q3W schedule expansion cohort (n=19).

The pharmacokinetic data from 31 subjects receiving 0.5 mg/kg to 10 mg/kg Q2W and 13 subjects receiving 2 mg/kg and 5 mg/kg Q3W has preliminarily proven that the drug exposure of BGB-A317 in the blood after a single dose increases linearly within the range of 0.5-10 mg/kg. The system clearance rate was 0.00789 L/h, volumes of distribution were 2.79 L and 1.44 L, and half-life was about 16 days.

Tumor types enrolled in the study included ovarian cancer (n=23), colorectal cancer (n=14), renal cell carcinoma (n=9), mesothelioma (n=7), urothelial carcinoma (n=6), cervical cancer (n=5), endometrial cancer (n=4), gastric cancer (n=4), cholangiocarcinoma (n=3), nasopharyngeal carcinoma (n=3), esophageal cancer (n=3), Merkel cell carcinoma (n=2), gallbladder cancer (n=2), pancreatic cancer (n=2), anal squamous cell carcinoma (n=2), sarcoma (n=2) and 1 subject each in other 9 tumor types. So far, only a limited number of subjects have received at least once effective efficacy evaluation. Based on the latest data, significant tumor shrinkage has been observed in several subjects with tumor types that are known to be sensitive to PD-1 antibody. Given the limited efficacy data and the fact that PD-1 antibody often shows features of lagging effect and pseudo-disease progression, the overall efficacy evaluation will be performed after more data becomes available.

In addition, a combination trial of BGB-A317 plus BGB-290 (PARP inhibitor) has been conducted in Australia. As of 5 May 2016, a total of 12 subjects received combination therapy of BGB-A317 with BGB-290. Among them, 1 subject in the 2 mg/kg Q3W BGB-A317 and 20 mg BID BGB-290 treatment group developed grade 4 immune-related liver disease, which was considered as a drug-related SAE by the investigator.

Clinical trials of other anti-PD-1 drugs suggest the most common AEs were grade 1/2, including arthralgia, cough, diarrhea, fatigue, fever, nausea, pruritus, and rash. However, grade 3/4 treatment-related AEs occurred in 15% of subjects in the early studies of nivolumab, and there were 3 deaths all due to pulmonary toxicity (Brahmer JR, 2010; Topalian SL, 2012). Grade 3/4 AEs were also reported in the pembrolizumab studies with one death due to myocardial infarction while being treated for pneumonitis/pneumonia (Hamid O, 2013). Drug-related AEs of special interest (AEs with potentially immune-related etiology) including vitiligo, pneumonitis, hepatitis, colitis, thyroiditis, and hypophysitis may be observed during multiple dose escalation in subjects with cancer. Currently the guidelines for management of immune-related adverse events have been developed and published (Bristol-Myers Squibb, 2012; Bristol-Myers Squibb, 2018), according to which clinicians may determine immune-related adverse reactions once they occur and provide appropriate management. For the irAEs during BGB-A317 treatment, please refer to the BGB-A317 IB.

1.5 Dose Determination in the Study

This study is a dose verification and indication expansion clinical trial of monoclonal antibody BGB-A317 conducted in Chinese patients with advanced malignant solid tumors, with a purpose of determining the safety, tolerability, pharmacokinetic characteristics and preliminary efficacy of BGB-A317 in Chinese patients with advanced solid tumors. Through dose verification as well as safety and efficacy expansion design parts, the study will determine the MTD and recommended Phase 2 dose (RP2D) of BGB-A317 in Chinese subjects.

This study is conducted on the basis of the multi-dose, dose-escalation Phase IA study conducted in Australia. According to preliminary results of the Phase IA clinical study in Australia (see Section 1.4),

0.5, 2, 5 and 10 mg/kg Q2W are all tolerable doses. In the dose-escalation stage, only 1 of the 22 subjects developed DLT, and the dose up to 10 mg/kg Q2W did not reach the MTD, so 10 mg/kg Q2W was determined as the maximum dosage. No apparent relationship was found between adverse reactions and doses. In addition, 2 mg/kg and 5 mg/kg were also explored in Q2W and Q3W administration settings, and the safety of each dose and the method of administration had been confirmed. From the safety data, drug-related adverse reactions from 2 mg/kg Q2W to 10 mg/kg Q2W were very similar. Overall, BGB-A317 has favorable tolerability at all dose levels, and slightly fewer adverse reactions occurred in the Q3W group.

According to the Phase IA pharmacokinetic data in Australia (see Section 1.4), plasma concentrations of BGB-A317 showed linear relationships with doses from 0.5 mg/kg Q2W to 10 mg/kg Q2W. Furthermore, according to the results of analysis of covariance, there was no significant correspondence between the weight of subjects and the *in vivo* clearance rate of BGB-A317. This conclusion supports the hypothesis of fixed-dose administration. Therefore, we have also begun to explore fixed-dose administrations in Australia and New Zealand. 200 mg Q3W and 300 mg Q3W have been chosen, which are equivalent to 3.3 mg/kg Q3W and 5 mg/kg Q3W (calculated with 60 kg) and still much lower than the maximum dose (10 mg/kg Q2W) studied in foreign trials even including extreme circumstances (eg, patients with low body weight). Therefore, 200 mg Q3W and 300 mg Q3W should be safe doses.

Up to September 30, 2016, 15 subjects from a total of 99 efficacy evaluable subjects (including various solid tumors) achieved confirmed response. These responders were dosed with 2mg/kg or 5mg/kg, Q2W or Q3W, and no clear dose-response correlation was observed. In view of safety data, pharmacokinetic data and limited preliminary anti-tumor efficacy data from previous studies, 200mg Q3W is currently recognized as RP2D. This study will further explore the safety and pharmacokinetic profiles of this dose in Chinese subjects during Phase I.

1.6 Manufacturing Process Change of BGB-A317

The manufacturing process and scale for BGB-A317 went through some changes during chemistry, manufacturing and controls (CMC) development. The original manufacturing process (OMP) was used to produce bulk drug substance (DS) under GMP condition at 100L and 500L scales, respectively. The investigational drug product (DP) made from the DS lots of IMP was used in phase I and II studies. Subsequently, the IMP was modified to the final manufacturing process (FMP), which was used to produce bulk DS under GMP condition at 500L and 2,000L scales, respectively. In parallel to the process change, specifications for the DS and DP purity were raised up, eg the requirement for monomeric faction by HP-SEC method was raised from 90% to 95% meanwhile all the compendial specifications/ standards were remained the same, in line with United States Pharmacopoeia, European Pharmacopoeia and Chinese Pharmacopoeia. The investigational DPs made by FMP either at 500L

scale or 2,000L scale are used for pivotal clinical studies. Due to the criticality of pivotal clinical studies, the process scale changes and deviations of investigational DPs made by 500L FMP and 2000L FMP, it is rationalized that pharmacokinetics profiles of the DPs made from 500L FMP and 2,000L FMP should be compared in human clinical study in addition to the comparability studies by the in vitro experiments.

2. STUDY OBJECTIVES

2.1 Primary Objectives

Phase I

Dose Verification study

- To assess the safety and tolerability of BGB-A317 in subjects with advanced solid tumors
- To determine the maximum tolerated dose (MTD), if any, and/or recommended Phase II dose (RP2D) for BGB-A317 in Chinese subjects

Pharmacokinetics (PK) sub-study

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the first dose of BGB-A317

  Notes: 500L-FMP indicates a final manufacturing process and scale of 500L; 2000L-FMP indicates a final manufacturing process and scale of 2000L.

- To assess the safety and tolerability of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP) in patients with advanced solid tumors

Phase II

- To assess the preliminary anti-tumor activity of BGB-A317

2.2 Secondary Objectives

Phase I

Dose Verification Study

- To characterize the pharmacokinetics of BGB-A317
- To assess the preliminary anti-tumor activity of BGB-A317
- To assess the host immunogenicity to BGB-A317

PK sub-study

- To assess the PK of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP) following the multiple doses of BGB-A317
- To assess the host immunogenicity to BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP)

- To assess the preliminary anti-tumor activities of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP)

Phase II

- To further assess the safety and tolerability of BGB-A317
- To further assess the pharmacokinetic characteristics of BGB-A317
- To assess the host immunogenicity to BGB-A317.

2.3 Exploratory Objectives

Phase I and Phase II

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Phase I

Dose Verification Study

- Safety and tolerability of BGB-A317: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events (AEs) and serious adverse events per the NCI-CTCAE Version 4.03 (Common Terminology Criteria Version 4.03, 2010), physical examination, electrocardiograms and laboratory assessments.
- The MTD (if any) and/or RP2D (s) for BGB-A317 will be determined based on safety, tolerability, pharmacokinetics, preliminary efficacy, and other available data.

Given the mechanism of BGB-A317 involving immune regulation, particular attention should be paid to irAEs which include pruritus, vitiligo, pruritic rash, macular rash, hypopigmentation, and other skin disorders; hypothyroidism and hyperthyroidism, hypophysitis, pneumonitis, hepatitis, nephritis, allergic rhinitis, diarrhea, abdominal pain, fatigue, hypersensitivity and any other irAEs. Researches should be done to exclude toxic, metabolic, infectious, neoplastic or other non-drug-related etiologic causes of such events.

PK sub-study

- PK: Single-dose pharmacokinetic parameters (C_{max}, AUC_{last}, and AUC_{inf}) will be assessed to evaluate the PK characteristics of BGB-A317 derived from both manufacturing processes and scales
- Safety: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events and serious adverse events per the NCI-CTCAE Version 4.03, physical examination, electrocardiograms, laboratory measurements

Phase II

- The ORR in different tumor types will be determined by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

3.2 Secondary Endpoints

Phase I

Dose Verification Study

- Evaluations of Pharmacokinetics: including but not limited to $AUC_{0\text{-}21\ day}$, C_{max} and time to maximum observed plasma concentration (T_{max}), minimum observed plasma concentration (C_{trough}), $t_{1/2}$, clearance (Cl) and volume of distribution during terminal phase (V_z)

- Evaluations of Efficacy: ORR, CR rate, PR rate, stable disease (SD) rate, progression-free survival (PFS), duration of response (DOR), and duration of SD will be determined by investigator per RECIST Version 1.1. Overall survival (OS) will be evaluated
- Anti-BGB-A317 antibodies: immunogenic responses to BGB-A317 will be assessed through the monitoring of the occurrence of anti-drug antibody

PK sub-study

- PK: Steady-state pharmacokinetic parameters (include but not limit to C_{trough}) will be assessed for both manufacturing processes and scales following the multiple doses of BGB-A317 to evaluate the PK characteristics at steady state
- Anti-BGB-A317 antibody: Immunogenic responses to BGB-A317 of both manufacturing processes and scales will be assessed to evaluate the comparability of the occurrence of anti-drug antibody
- Efficacy evaluations: ORR, CR rate, PR rate, SD rate, PFS, and DOR and duration of SD will be determined by investigator based on RECIST Version 1.1; OS will be evaluated

Phase II

- Evaluations of Efficacy: CR rate, PR rate, SD rate, PFS, duration of response, duration of SD, disease control rate (DCR) and clinical benefit rate (CBR) will be determined by investigator based on RECIST Version 1.1; OS will be evaluated
- Safety and tolerability of BGB-A317: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events and serious adverse events per NCI-CTCAE Version 4.03, physical examination, electrocardiograms and laboratory assessments
- Evaluations of Pharmacokinetics: including but not limited to C_{trough}
- Anti-BGB-A317 antibodies: immunogenic responses to BGB-A317 will be assessed by monitoring the occurrence of anti-drug antibody (ADA)

3.3 Exploratory Endpoints

[redacted]

4. INVESTIGATIONAL PLAN

4.1 Study Design

This study is a dose verification, PK assessment of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP; FMP: Final Manufacturing Process) and indication expansion clinical study of monoclonal antibody BGB-A317 conducted in Chinese subjects with advanced solid tumors, with a purpose of exploring the safety, tolerability, pharmacokinetics and preliminary efficacy. This study is carried out on the basis of a Phase IA multi-dose and dose-escalation study in Australia. According to the preliminary results of the Phase IA clinical study in Australia, 0.5, 2, 5 and 10 mg/kg, Q2W are all tolerable doses. In addition, 2 and 5 mg/kg, Q3W have also been confirmed as tolerable doses.

This study will be carried out in two stages. Phase I is a dose verification and PK assessment of products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP, FMP = Final Manufacturing Process) study and Phase II is an indication expansion study. All subjects will receive BGB-A317 until they have no evidence of continued clinical benefits, unacceptable toxicity, or withdrawal of informed consent in the discretion of the investigator. Paraffin-embedded tumor tissue will be collected for purpose of [redacted]. However, if there is clinically appropriate biopsy lesion (biopsy is a must in specific cancer types in Phase II), a fresh tumor biopsy at baseline is strongly recommended. For these subjects, if possible, a biopsy for potential [redacted] after two cycles of treatment is strongly recommended. A written informed consent form (ICF) is required for fresh tumor biopsies.

Subjects will be monitored for safety, anti-BGB-A317 antibodies and efficacy throughout the study. Radiological assessment of tumor-response status should be performed approximately every 9 weeks in the first year, then every 12 weeks thereafter.

A flow chart of the study design is presented in Appendix 1.

4.1.1 Phase I

Phase I study is a multicenter and open-label study including a dose verification study and a PK sub-study of both manufacturing processes and scales of BGB-A317 (500L-FMP and 2000L-FMP)

Dose Verification study (using BGB-A317 produced by 500L-OMP,)

3-6 subjects will be enrolled firstly to assess DLT.

- If none of the 3-6 subjects experience a DLT at the setting dose, enrollment will be continued until about 20 subjects are enrolled in total.
- 3 additional subjects will be enrolled if a DLT is observed in 1 of 3 subjects; 2 additional subjects will be enrolled if a DLT is observed in 1 of 4 subjects; and 1 additional subject will be enrolled if a DLT is observed in 1 of 5 subjects. No additional subjects are required if a DLT is observed in 1 of 6 subjects.

- If 2 or more subjects develop DLT among 3-6 subjects in the cohort, the dose level will be considered as exceeding the MTD. All investigators will be informed of such dose level.

DLT assessments will be assessed among evaluable subjects in Cycle 1 (1-21 days) (refer to Section 4.2 for detailed assessment standard). An evaluable subject is defined as one who has received at least 80% of the first dose and completed all safety assessments required in Cycle 1, or any subject who has experienced DLT in Cycle 1.

A Safety Monitoring Committee (SMC) will be established by the sponsor and investigators. SMC will recommend RP2D based on the safety and pharmacokinetics of BGB-A317, if necessary, and decide whether to add unscheduled doses for trial.

Dose level

According to the safety results of the dose-escalation trial on BGB-A317 conducted in Australia, this study will assess the safety and pharmacokinetic characteristics of flat-dose 200 mg Q3W in Chinese patients with advanced malignant solid tumors, and other doses may be further explored based on the safety result and necessity.

Among the 3-6 subjects in the 200 mg Q3W cohort, if 2 or more subjects experience DLT in Cycle 1, such starting dose will be considered as exceeding the MTD, and a lower dose, such as 100 mg Q3W, will be assessed in 3-6 subjects.

If dose 200 mg passes the DLT assessment, the cohort at such dose can be expanded to about 20 subjects to further assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamic characteristics of BGB-A317. In order to continuously monitor safety, when the cohort has been expanded to 10 subjects and ⩾33% of them has experienced DLT within 21 days in Cycle 1, enrollment will be suspended, and an SMC meeting will be immediately held to discuss and determine whether such dose is safe.

PK sub-study: It is a parallel and multiple doses study, which analyzes the PK and safety of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP). DLT and RP2D of all subjects are not assessed.

Total 48 subjects (24 per arm) are planned to be enrolled to receive treatment of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP). Cycle 1 lasts for 28 days, and Cycle 2 and those thereafter last for 21 days. If there is any drop-out before the complete of the first treatment cycle (28 days) of intensive PK, additional subjects will be enrolled until for each arm there are total 24 subjects complete the first treatment cycle. PK, safety and preliminary anti-tumor activity are analyzed between the two arms of patients. Schematic of the trial design is shown in Appendix 1.

4.1.2 Phase II

To further assess the efficacy of BGB-A317 in Chinese patients with malignant solid tumors, once 200 mg Q3W has been confirmed as a tolerable dose in Chinese population and determined as RP2D,

an indication-expansion study will be carried out among the following 11 arms of indications (the inclusion and exclusion criteria for each group of indications are shown in Section 5.1). Because of the changes of the manufacturing processes and scales during study, BGB-A317 of two manufacturing processes and scales (500L-OMP and 2000L-FMP) will be used for this Phase II study.

Arm 1: Melanoma

Arm 2: Non-small cell lung cancer (PD-L1 positive)

Arm 3: Non-small cell lung cancer (PD-L1 negative)

Arm 4: Gastric cancer

Arm 5: Esophageal cancer

Arm 6: Renal cell carcinoma

Arm 7: Urothelial carcinoma

Arm 8: Microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) CRC

Arm 9: Triple negative breast cancer, head and neck squamous cell carcinoma (HNSCC), small cell neuroendocrine carcinoma, or other tumors with MSI-H or dMMR

Arm 10: Nasopharyngeal carcinoma (NPC)

Arm 11: Hepatocellular Carcinoma (HCC), excluding mixed hepatocellular and cholangiocellular carcinoma.

In the indication-expansion study, about 20 subjects are enrolled into each arm. For tumors that are difficult to enroll, the sponsor may early terminate the enrollment of subjects in this arm. The statistical basis for the number of subjects enrolled in each arm of phase II will be specified in the statistical plan.

To fully assess the safety of BGB-A317, the contract research organization (CRO) and medical monitor from the sponsor will regularly review the safety data, and if necessary, will convene an interim SMC meeting.

If subjects with a certain kind of tumor experience significant toxicities in the dose-extension stage, the investigator and the sponsor will discuss and decide whether to conduct an independent study or to terminate the study in such tumor indications.

4.2 Dose-Limiting Toxicity

All toxicities or AEs will be graded according to the NCI-CTCAE Version 4.03. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to study drug administration:

Non-hematologic:

1. Grade 4 or above toxicity.

2. Grade 3 toxicity (regardless of the duration), except for laboratory abnormalities, diarrhea, nausea, vomiting and asymptomatic biochemical abnormalities that improve to Grade 2 or lesser severity within 3 days of best supportive care.

3. Grade 3 adverse event of tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor) lasting > 7 days.

4. Grade 3 or above irAE.

Hematologic:

1. Grade 4 neutropenia lasting > 7 days.

2. Febrile neutropenia (defined as absolute neutrophil count [ANC] < $1000/mm^3$ with a single temperature of 38.3°C or a sustained temperature of 38°C for > 1 hour).

3. Grade 3 neutropenia with infection.

4. Grade 3 thrombocytopenia with bleeding.

5. Grade 4 thrombocytopenia.

6. Grade 4 anemia (life-threatening).

And any other grade toxicity which requires premature withdrawal of the subject from the study upon discussion of investigator and sponsor.

Subjects who received < 80% of the BGB-A317 infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion-related reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will need to be replaced.

Resumption of BGB-A317 administration for subjects experiencing DLTs may be permitted according to the criteria described in Section 4.3, if clinically appropriate, contingent on the restoration of the DLT to ⩽ Grade 0-1 severity and interruption or delay of treatment for no more than 12 weeks.

4.3 Dose Modifications, Dose Delay and Missing Dose

If an infusion cannot be administered at a scheduled visit, due to holiday, weekend, or other events (eg, AE), it must be administered as soon as possible. Each treatment cycle is 21 (± 3) days. Generally, subjects with infusion delays ⩽ 10 days, the infusion/administration will always be performed as scheduled. For delays > 10 days, the infusion/administration will be performed according to the next scheduled dose (consulting with the sponsor for details if needed). Patients with infusion delays > 84 days (12 weeks) for Q3W schedule should discontinue treatment and enter the Follow-up Period with the exception of delays related to prophylactic vaccinations or after specific discussion and alignment between the investigator and medical monitor in settings where benefit/risk may justify

continued study therapy (eg, subject deriving clinical benefit who requires prolonged steroid taper for treatment of non-DLT irAEs).

BGB-A317 will be withheld for irAEs according to dose modification described in Appendix 3. BGB-A317 dosing can be resumed for subjects whose adverse reaction has recovered to Grade 0-1 within 12 weeks after last administration. Dose reduction is not allowed in this study.

Two dosing delays due to toxicity will be permitted. In the event of a third occurrence of a toxicity which would require dosing delay, study therapy will be discontinued permanently after consultation with the sponsor. For subjects who have delayed administration for more than 6 weeks due to reasons other than treatment toxicity (eg, poor adherence), the investigator will decide whether to discontinue the patient's participation after consultation with the medical monitor.

BGB-A317 will be permanently discontinued for irAEs as specified in Appendix 3. In case a subject is benefiting from the study treatment while meeting the discontinuation criteria described, discussion between sponsor and investigator will be conducted to make a decision that will be in the best interest of the subject.

Refer to Appendix 3 for more details about irAEs and management of such events.

4.4 End of Treatment Visit

The End of Treatment (EOT) Visit should ideally occur $\leqslant$ 7 days after study drug is permanently discontinued, typically after progressive disease (PD) is documented. If routine laboratory tests (eg, hematology, clinical chemistry) is completed $\leqslant$ 7 days before the EOT Visit, these tests do not need to be repeated. The EOT Visit may occur later, eg, if study drug was initially held for AEs to then be permanently discontinued. If the EOT Visit cannot occur until 30 days (± 7 days) after last dose of study drug, the EOT Visit may also be used as the Safety Follow-up Visit. Tumor assessment is not required at the End of Treatment Visit provided that fewer than 6 weeks have passed since the last assessment.

See Section 4.5 for assessments to be performed for the EOT Visit.

4.5 Schedule of Assessment

The schedule of Phase I study assessments is presented in Table 1, the pharmacokinetic sampling schedule for dose verification study of Phase I in Table 2 and the sampling schedule for PK sub-study of Phase I in Table 3. The schedule of Phase II study assessments is presented in Table 4.

Table 1. Schedule of Phase I Study Assessments.

Phase I	Screening[1]	Treatment Period													Safety Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days or 28 days)[2]						Cycle 2 and subsequent cycles (except for Cycle 5) (21 days)	Cycle 5 (21 days)					End of Treatment Visit[3]		
Days	-28 ~ -1	1	2	4 (or 5)	8	15±1	22±1	1±3	1±3	2	4 (or 5)	8	15±1	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Informed consent[6]	x															
Inclusion/exclusion criteria	x															
Demographic/Medical History/Prior Medications[7]	x															
Vital signs/Weight[8]	x	x	x	x	x	x	x	x	x					x	x	
Physical examination	x	x						x	x						x	
ECOG performance status	x	x						x	x						x	
12-lead ECG[9]	x	As clinically indicated													x	
Ultrasonic echocardiography	x	As clinically indicated														

Phase I	Screening[1]	Treatment Period													Safety Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days or 28 days)[2]						Cycle 2 and subsequent cycles (except for Cycle 5) (21 days)	Cycle 5 (21 days)					End of Treatment Visit[3]		
Days	-28 ~ -1	1	2	4 (or 5)	8	15±1	22±1	1±3	1±3	2	4 (or 5)	8	15±1	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Adverse events (serious adverse events)[10]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	
Concomitant medication	x	x			x	x	x	x	x					x	x	
CBC with differential[11]	x[1]	x			x	x	x	x	x					x[3]	x	
Serum Chemistry[11]	x[1]	x			x	x	x	x	x					x[3]	x	
Coagulation Parameters[12]	x	As clinically indicated													x	
Urinalysis[11]	x[1]	x			x	x	x	x	x					x[3]	x	
Pregnancy test[13]	x															
Thyroid function[14]	x[1]	x						x[14]	x						x	
Anti-BGB-A317 antibodies[15]		x						x[15]	x						x	

Phase I	Screening[1]	Treatment Period													Safety Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days or 28 days)[2]						Cycle 2 and subsequent cycles (except for Cycle 5) (21 days)	Cycle 5 (21 days)					End of Treatment Visit[3]		
Days	-28 ~ -1	1	2	4 (or 5)	8	15±1	22±1	1±3	1±3	2	4 (or 5)	8	15±1	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Pharmacokinetics in Dose verification study[16]		x	x	x	x	x		x[16]	x	x	x	x	x		x	
Pharmacokinetics in PK sub-study[17]		x	x	x	x	x	x	x[17]	x	x		x	x		x	
HBV/HCV tests[18]	x															
Tumor imaging[19]	x							x[19]						x		
Study drug administration		x						x	x							
Archival tumor tissues[20]	x															
Fresh tumor tissues[21] (additional consent required)	x							x[21]								
Survival status																x

Phase I	Screening[1]	Treatment Period													Safety Follow-up[4]	Survival Follow-up[5]
		Cycle 1 (21 days or 28 days)[2]						Cycle 2 and subsequent cycles (except for Cycle 5) (21 days)	Cycle 5 (21 days)					End of Treatment Visit[3]		
Days	-28 ~ -1	1	2	4 (or 5)	8	15±1	22±1	1±3	1±3	2	4 (or 5)	8	15±1	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Pulmonary function tests[22]	x	As clinically indicated														

Abbreviations: aPTT, activated partial thromboplastin time; CBC, complete blood count; CR, complete response; CT, computed tomography; DLT, dose-limiting toxicity; ECG, Electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FMP, final manufacture process; FT3, free T3; FT4, free T4; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MRI, magnetic resonance imaging; PD, progressive disease; PK, pharmacokinetics; PR, partial response; PT, prothrombin time; TSH, thyroid-stimulating hormone.

Note:

1. All tests (except collection of fresh biopsy samples) in the screening period should be performed within 28 days prior to first dosing. If hematology, serum chemistry, urinalysis, and thyroid function tests are completed within 3 days before C1D1 administration, it is not necessary to conduct these tests again on C1D1.
2. The duration of the first cycle for the first 20 subjects will be 21 days, and DLT will be conducted in this period; the duration of the first cycle for the rest 48 subjects will be 28 days, which will be performed for the PK analyses of products derived from two manufacturing processes and scales (500L-FMP vs 2000L-FMP),
3. The End of Treatment Visit is conducted when the investigator determines that the study drug will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, it is not necessary to assess again. Tumor assessment is not required at the End of Treatment Visit provided that fewer than 6 weeks have passed since the last assessment.
4. The 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. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first. The EOT Visit at which a response assessment showed PD, resulting in patient discontinuation from treatment, may be used as the Safety Follow-up Visit if it occurred 30 days (± 7 days) after the last dose of study drug.

5. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the sponsor.
6. Written consent must be obtained prior to performing any protocol specific procedure. Results of an imaging 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). Assign subject number when the study informed consent is signed.
7. 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. Report complete medication history for 30 days prior to the screening visit (Visit 1).
8. Vital signs include temperature, pulse, respiratory rate and blood pressure.
9. Electrocardiogram (12-lead ECG) should be performed at the following time points: within 28 days prior to Cycle 1 Day 1 (screening period) and the evaluation result is used as the baseline; and at the Safety Follow-up visit. Additional ECGs may be performed if clinically indicated (refer to Section 8.3.3).
10. Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03 **(NCI-CTC, June 2010).** Characterization of toxicities will include severity, duration, and time to onset. All adverse events, including SAEs, will be collected as described in Section 10.6. At the end of treatment, ongoing adverse events considered related to study treatment will be followed until the event has resolved to baseline or grade $\leqslant$ 1, the event is assessed by the investigator as stable, the patient is lost to follow up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.
11. Routine laboratory tests (eg, CBC with differential; serum chemistry; urinalysis) should be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis should be collected up to 3 days prior to Day 1 of any Cycle.
12. PT/INR and aPTT should be collected at Screening and at the Safety Follow-up Visit after discontinuation of study therapy. When clinically indicated, coagulation parameters should be assessed. PT/INR and aPTT will be analyzed by the local study center's laboratory.
13. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days of the first investigational product administration). Subsequent examinations should be implemented if clinically indicated. Serological tests are not required if subsequent urine pregnancy test is negative.
14. FT3, FT4 and TSH are analyzed in the screening period and up to 3 days before dosing on Day 1 every cycle during the first 17 cycles, approximately every 2 cycles thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.
15. **Dose verification study:** Blood for anti-BGB-A317 antibodies should be collected within 60 minutes before infusion on Day 1 in Cycle 1, 2, 3, 5, 7, 9, 13, 17, about every 8 cycles thereafter; **PK sub-study:** Blood for anti-BGB-A317 antibodies should be collected within 60 minutes before infusion on Day 1 in Cycle 1, 2, 3, 5, 7, 9, 17, about every 8 cycles thereafter; and blood collection for assessing anti-BGB-A317 antibodies in both studies at the Safety Follow-Up Visit are required. In subjects who discontinue study therapy before 6 months, every effort should be made to analyze anti-BGB-A317 antibodies approximately 6 months after the first dose. Analysis will be performed by the central laboratory designated by the sponsor.
16. Applicable to the first 20 subjects in the dose verification study. Refer to Table 2 for details on timing of pharmacokinetics sample collection. Procedures for collection of samples are described in the Lab Manual.
17. Applicable to the rest 48 subjects in the PK sub-study comparing products derived from two manufacturing processes and scales (500L-FMP and 2000L-FMP). Refer to Table 3 for details on timing of pharmacokinetics sample collection. Procedures for collection of samples are described in the Lab Manual.
18. Testing will be performed by the local laboratory at Screening. It includes Hepatitis C virus (HCV) antibody, HBsAg and HBcAb. All HbsAg or HCV positive subjects at screening must pass the test of Hepatitis B virus (HBV) DNA titres (< 2500 copies [cps]/mL or 500 IU/mL) and HCV RNA (below the lower limit of the assay) before being enrolled to exclude active hepatitis B or hepatitis C virus infection. Subjects with positive HBV DNA at screening

should be repeated periodically during the study if clinically indicated.

19. Tumor imaging (either contrast-enhanced CT or MRI) will be performed within 28 days prior to enrollment, and while on study approximately every 9 weeks (±7 days) in the first 17 cycles, approximately every 12 weeks (±7 days) thereafter. If tumor imaging is completed within 6 weeks before the End of Treatment Visit, it is not necessary to assess again at the End of Treatment Visit. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next scheduled time point will be used for response confirmation. Progressive disease (PD) suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next scheduled time point (but not to exceed 12 weeks), before discontinuation of study treatment. Subjects who stop treatment prior to documentation of disease progression will undergo repeated imaging every 9 weeks for tumor response assessments as described in Section 8.3.6 and Section 8.6.1.
20. Archival tumor tissue must be collected for purpose of [redacted] (this should be emphasized in the subject's informed consent). See Section 8.9.
21. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 42 days before starting treatment) is mandatory (written subject's consent is required prior to fresh tumor biopsies). Baseline or paired fresh tumor biopsies are strongly recommended for potential predictive, prognostic, or [redacted] in subjects with readily accessible tumor lesions and who consent to the biopsies. Subjects who consent to paired biopsies should undergo biopsies after two cycles (approximately on Cycle 3 Day 1). See Section 8.9.
22. Patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer will have pulmonary function testing which may including but is not limited to spirometry and assessment of diffusion capacity done during the screening period, to assist the determination of suitability for enrollment on the study.

Table 2. Pharmacokinetic Sampling and ADA Test for dose verification study of Phase I

Phase I		Week	Day		PK sampling Time Points	ADA Test Time Points
Treatment Period	Cycle 1 （21 days，DLT period）	1	1	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
					90 mins[2]	
					360 mins[3]	
			2		24 hours[3]	
			4（or 5）		72（or 96）hours[3]	
			8			
			15 ± 1			
	Cycle 2（21 days）	4	22 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Cycle 3（21 days）	7	43 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Cycle 5（21 days）	13	84 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
					90 mins[2]	
					360 mins[3]	
			2		24 hours[3]	
			4（or 5）		72（or 96）hours[3]	
			8			
			15 ± 1			

	Cycle 6（21 days）	16	106 ± 3	Predose	-60 min to 0 hour	
				Postdose	End of infusion to 30 mins[1]	
	Cycle 7（21 days）	19	127 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Cycle 9（21 days）	25	169 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Cycle 13（21 days）	37	253 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Cycle 17（21 days）	49	337 ± 3	Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
	Every 8 cycles	Every 24 weeks		Predose	-60 mins to 0 hour	-60 mins to 0 hour
				Postdose	End of infusion to 30 mins[1]	
Safety Follow-up	(30 ± 7 days after last dose)					

Abbreviations: ADA, anti-drug antibody; DLT, dose limiting toxicity; irAE, immune-related adverse event; PK, pharmacokinetics.

Please note: Actual drug dosing and PK sampling times must be documented by the study center and will be captured in the database.

1. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

2. Window: ± 20 minutes.

3. Window: ± 1 hour.

If a subject presents with a DLT or any grade 3 or above irAE (refer to Appendix 3), additional blood PK samples will be taken to determine the serum concentration of BGB-A317.

Table 3. Pharmacokinetic Sampling and ADA Test Schematic of PK Sub-study of Phase I

Phase I		Week	Days		Timepoints of Blood sampling	Timepoints of ADA analyses
Treatment Period	Cycle 1 (28 days)	1	1	Pre-dose	-60 min to 0 min	-60 min to 0 min
				End of infusion	End of infusion to 30 min[1]	Day 22
					3 hours[2]	
					6 hours[2]	
					Day 2[3]	
					Day 4[4]	
					Day 8[4]	
					Day 15[4]	
					Day 22 [4]	
	Cycle 2（21 days）	5	29 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
	Cycle 3（21 days）	8	50 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
				End of infusion	End of infusion to 30 min[1]	
	Cycle 25（21 days）	14	92 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
				End of infusion	End of infusion to 30 min[1]	
					Day 2[3]	
					Day 8[4]	
					Day 15[4]	
	Cycle 6（21 days）	17	113 ± 3	Pre-dose	-60 min to 0 min	
	Cycle 7（21 days）	20	134 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
				End of infusion	End of infusion to 30 min[1]	
	Cycle 9（21 days）	26	176 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min

				End of infusion	End of infusion to 30 min[1]	
	Cycle 17（21 days）	50	344 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
	Cycle 25（21 days）	74	512 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
	Cycle 33（21 days）	98	680 ± 3	Pre-dose	-60 min to 0 min	-60 min to 0 min
	Every 8 cycles	Every 24 weeks		Pre-dose	-60 min to 0 min	-60 min to 0 min
Safety Follow-up	(30 ± 7 days after last dose)					

Abbreviations: ADA, anti-drug antibody; irAE, immune-related adverse event; PK, pharmacokinetics.

Please note: Actual drug dosing and PK sampling times must be documented by the study center and will be captured in the database.

1. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

2. Window: ±20 minutes.

3. Window: ±2 hours.

4. Window: ±1 day

If a subject presents with an any grade 3 or above irAE (refer to Appendix 3), additional blood PK samples will be taken to determine the serum concentration of BGB-A317.

Table 4. Phase II Study Assessments and Procedure Schedule

Phase II	Pre-screening	Screening[1]	Treatment Period			Safety Follow-up[3]	Survival Follow-up[4]
			Cycle 1 (21 days, DLT assessment period)	Cycle 2 and Subsequent cycles (Every 21 days)	End of Treatment Visit[2]		
Days	56 days before screening	-28 ~ -1	1±3	1±3	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Informed consent[5]	x	x					
Inclusion/exclusion criteria		x					
Demographic/Medical History/Prior Medications[6]	x	x					
Vital signs/Weight[7]		x	x	x	x	x	
Physical examination		x	x	x		x	
ECOG performance status		x	x	x		x	
12-lead ECG[8]		x	As clinically indicated			x	
Adverse events (serious adverse events)[9]	x	x	x	x	x	x	
Concomitant medications		x	x	x	x	x	
CBC with differential[10]		x[1]	x	x	x[2]	x	
Serum chemistry[10]		x[1]	x	x	x[2]	x	
Coagulation parameters[11]		x	As clinically indicated			x	
Urinalysis[10]		x[1]	x	x	x[2]	x	
Pregnancy test[12]		x					

Phase II	Pre-screening	Screening[1]	Treatment Period			Safety Follow-up[3]	Survival Follow-up[4]
			Cycle 1 (21 days, DLT assessment period)	Cycle 2 and Subsequent cycles (Every 21 days)	End of Treatment Visit[2]		
Days	56 days before screening	-28 ~ -1	1±3	1±3	0 to 7 days	30 ± 7 days after last dose	Every 3 months
Thyroid function[13]		x[1]	x	x[13]		x	
Anti-BGB-A317 antibodies[14]			x	x[14]		x	
Pharmacokinetics[15]			x	x[15]		x	
HBV/HCV tests[16]		x					
Tumor imaging[17]		x		x[17]	x		
Study drug administration			x	x			
Archival tumor tissues[18] (additional consent required)	x	x					
Fresh tumor tissues[19] (additional consent required)	x	x		x[19]			
Blood samples required for MSI/MMR mutation testing[20]	x	x					
Survival status							x
Pulmonary function tests[21]		x	As clinically indicated				

Abbreviations: aPTT, activated partial thromboplastin time; CBC, complete blood count; CR, complete response; CT, computed tomography; DLT, dose-limiting toxicity; ECG, Electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT, end of treatment; FT3, free T3; FT4, free T4; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen;.HBV=Hepatitis B virus; HCV=Hepatitis C virus; INR, international normalized ratio; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD, progressive disease; PR, partial response; PT, prothrombin time; TSH, thyroid-stimulating hormone.

Note:

1. All tests (except collection of fresh biopsy samples) in the screening period should be performed within 28 days prior to 1st dosing. If hematology, serum chemistry, urinalysis, and thyroid function are completed within 3 days before C1D1 administration, it is not necessary to conduct these tests again on C1D1.
2. The End of Treatment Visit is conducted when the investigator determines that the study drug will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the End of Treatment Visit, it is not necessary to assess again. Tumor assessment is not required at the End of Treatment Visit provided that ⩽ 6 weeks have passed since the last assessment.
3. The Safety Follow-Up visit should be conducted 30 days (± 7 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first. The EOT Visit at which a response assessment showed PD, resulting in patient discontinuation from treatment, may be used as the Safety Follow-up Visit if it occurred 30 days (± 7 days) after the last dose of study drug.
4. Following completion of the treatment and Safety Follow-up phases of the study, every effort should be made to follow up all subjects for their survival status until subject death or termination by the sponsor.
5. Written consent must be obtained prior to performing any protocol specific procedure. Results of an imaging 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). Assign subject number when the study informed consent is signed.
6. 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. Report complete medication history for 30 days prior to the screening visit (Visit 1).
7. Vital signs include temperature, pulse, respiratory rate and blood pressure.
8. Electrocardiogram (12-lead ECG) should be performed at the following time points: within 28 days prior to Cycle 1 Day 1 (screening period) and the evaluation result is used as the baseline; and at the Safety Follow-up visit. Additional ECGs may be performed if necessary (refer to Section 8.3.3).
9. Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03 (NCI-CTC, June 2010). Characterization of toxicities will include severity, duration, and time to onset. All adverse events, including SAEs, will be collected as described in Section 10.6. At the end of treatment, ongoing adverse events considered related to study treatment will be followed until the event has resolved to baseline or grade ≤ 1, the event is assessed by the investigator as stable, the patient is lost to follow up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.
10. Routine laboratory tests (eg, CBC with differential; serum chemistry; urinalysis) should be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis should be collected up to 3 days prior to Day 1 of any Cycle.
11. PT/INR and aPTT should be collected at Screening and at the Safety Follow-up Visit after discontinuation of study therapy. When clinically indicated, coagulation parameters should be assessed. PT/INR and aPTT will be analyzed by the local study center's laboratory.
12. Only in women of childbearing potential. Subjects must have a negative serum pregnancy test at screening (within 7 days of the first investigational product administration). Subsequent examinations should be implemented if clinically indicated. Serological tests are not required if subsequent urine pregnancy test is negative.
13. FT3, FT4 and TSH are analyzed in the screening period and within 3 days before dosing on Cycle 1 Day 1, Cycle 2 Day 1 and Day 1 of every 2 cycles thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.

14. Blood for anti-BGB-A317 antibodies should be collected within 60 minutes before infusion on Day 1 in Cycle 1, 2, 5, 9, 13, 17, 25, about every 8 cycles thereafter, and at the Safety Follow-Up Visit. Analysis will be performed by the central laboratory designated by the sponsor.
15. Pharmacokinetics samples will be collected 60-minute predose and about 30-minute postdose on Day 1 of Cycle 1, 2, 5, 9, 13, 17, 25, about every 8 cycles thereafter, and at the Safety Follow-Up Visit. Procedures for collection of samples are described in the Lab Manual.
16. Testing will be performed by the local laboratory at Screening. It includes Hepatitis C virus (HCV) antibody, HBsAg and HBcAb. All positive HbsAg at screening or Arm 11 subjects must pass the test of Hepatitis B virus (HBV) DNA titres (< 2500 copies [cps]/mL or 500 IU/mL) before being enrolled; Positive HCV antibody subjects must pass the HCV RNA test (below the lower limit of the assay) before being enrolled (section 5.2). Subjects with positive HBV DNA at screening should be repeated periodically during the study if clinically indicated.
17. Tumor imaging (either contrast-enhanced CT or MRI, preferentially CT) will be performed within 28 days prior to enrollment, and while on study approximately every 9 weeks (±7 days) in the first 17 cycles, approximately every 12 weeks (±7 days) thereafter. If tumor imaging is completed within 6 weeks before the End of Treatment Visit, it is not necessary to assess again at the End of Treatment Visit. The same imaging technique should be used in a subject throughout the study. After first documentation of response (CR or PR), imaging performed at the next scheduled time point will be used for response confirmation. PD suspected as pseudo-progression needs to be confirmed in a subsequent imaging at least 4 weeks later or at the next scheduled time point (but not to exceed 12 weeks), before discontinuation of study treatment. Subjects who stop treatment prior to documentation of disease progression will undergo repeated imaging every 9 weeks for tumor response assessments as described in Section 8.3.6 and Section 8.6.1.
18. Archival tumor tissue must be collected for purpose of [redacted] (this should be stressed in the subject's informed consent). For subjects to be enrolled in Arm 8, if their MMR/MSI-mutation status is unknown, corresponding tests must be performed during prescreening period - 56 days (8 weeks) prior to screening period. If archival tissue samples have been collected during pre-screening period, no additional collection is required during screening period. See Section 8.9.
19. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at baseline (within 42 days before treatment starts) is mandatory (written subject's consent is required prior to fresh tumor biopsies). For subjects to be enrolled in Arm 8, if their MMR/MSI-mutation status is unknown and subjects do not have archival tumor tissues, fresh tumor biopsy samples must be collected during pre-screening period - 56 days (8 weeks) prior to screening for corresponding tests. If sufficient number of tumor tissue samples have been collected during pre-screening period, no additional collection is required during screening period. Baseline or paired fresh tumor biopsies are strongly recommended for potential predictive, prognostic, or [redacted] in subjects with readily accessible tumor lesions and who consent to the biopsies. If feasible, subjects in Arm 1 must undergo baseline tumor biopsy (biopsy is not required for subjects who provide archival tissue samples obtained within 12 weeks before treatment starts). Subjects who consent to paired biopsies should undergo biopsies after two cycles (approximately on Cycle 3 Day 1). See Section 8.9.
20. For subjects to be enrolled in Arm 8, if their MSI/MMR-mutation status is unknown, blood samples must be collected during pre-screening period - 56 days, (8 weeks) prior to screening period, for MSI/MMR-mutation pre-screening. See Section 8.9.
21. Patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer will have pulmonary function testing which may including but is not limited to spirometry and assessment of diffusion capacity done during the screening period, to assist the determination of suitability for enrollment on the study.

5. STUDY POPULATION

5.1 Inclusion Criteria

Subjects eligible for study must meet all following criteria:

1. Voluntarily signed informed consent form for the study
2. Aged ⩾ 18 years on the day of signing informed consent
3. Subjects must have a histologically or cytologically confirmed advanced or metastatic tumor (unresectable), have had progression or intolerability since last standard anti-tumor treatment, or have no available standard treatment or have refused standard therapy, as well as meet following requirements for tumor types in the corresponding stages:
    a) Phase I: Including but not limited to non-small cell lung cancer (NSCLC), melanoma, gastric cancer, esophageal carcinoma, ovarian cancer, urothelial carcinoma, head and neck squamous cell carcinoma (HNSCC), renal cell carcinoma (RCC) and triple negative breast cancer (TNBC)
    b) Phase II:
        - Arm 1 - melanoma, excluding uveal or ocular melanoma
        - Arm 2 - NSCLC (PD-L1 positive) and Arm 3—NSCLC (PD-L1 negative):
            i. PD-L1 expression must be tested prospectively at the central laboratory designated by the sponsor (refer to Section 8.9 for the definition of PD-L1 positive)
            ii. Subjects with known EGFR mutations (EGFR detection methods and results need to be approved by the study site) are excluded; subjects with non-squamous carcinoma of unknown EGFR mutations must be tested prospectively at the central laboratory designated by the sponsor; and if the EGFR mutations are positive, the subjects are excluded
            iii. Subjects with known *ALK* gene rearrangements are excluded
        - Arm 4 - gastric cancer: gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma)
        - Arm 5 - esophageal carcinoma: esophageal squamous cell carcinoma
        - Arm 6 - RCC: RCC containing the component of clear cell
        - Arm 7 - urothelial carcinoma: locally advanced or metastatic urothelial transitional cell carcinoma (including renal pelvis, ureter, bladder and urethra)
        - Arm 8 - MSI-H or dMMR CRC: subjects with documented MSI-H or dMMR are eligible if tumor samples and blood samples are provided for retrospective analyses at the central laboratory designated by the sponsor; subjects with unknown MSI or MMR status must be tested prospectively before enrollment at the central laboratory designated by the sponsor (refer to Section 8.1)
        - Arm 9 - TNBC, HNSCC, small cell neuroendocrine carcinoma (SCNEC) or other tumors with known MSI-H or dMMR (subjects with documented MSI-H or dMMR are

eligible if tumor samples and blood samples are provided for retrospective analyses at the central laboratory designated by the sponsor, refer to Section 8.9 for detection methods)

- Arm 10 - nasopharyngeal carcinoma (NPC): WHO type II-III (differentiated-non-keratinizing type and undifferentiated-non-keratinizing type)
- Arm 11 - Child-Pugh Grade A hepatocellular carcinoma (See Appendix 2, excluding mixed hepatocellular and cholangiocellular carcinoma

4. Subjects must be able to provide archival tumor tissues (paraffin blocks or at least 10 unstained tumor specimen slides; subjects may be permitted to be enrolled on a case-by-case basis after discussion with medical monitors from the sponsor if less than 10 unstained slides are provided) or newly obtained tumor tissue that has not been radiated, and relevant pathological reports. Refer to Section 8.9 for the requirements for tumor samples
   For subjects who have easily accessible lesions and consent to biopsies, fresh baseline or paired tumor biopsies are strongly recommended for [redacted]. For **Arm 1 (melanoma)** in Phase II, tumor biopsies must be performed at baseline if feasible (biopsy is not required for subjects who provide archival tissue samples obtained within 12 weeks before treatment starts). Subjects may be permitted to enroll on a case-by-case basis after discussion with the medical monitors if biopsy specimens are not available
5. Subjects must have at least one measurable lesion as defined per RECIST Version 1.1
6. Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 1$
7. Life expectancy $\geqslant 12$ weeks
8. Subject must have adequate organ function as indicated by the following laboratory values
   a) Absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L
   b) Platelets $\geqslant 75 \times 10^9$/L
   c) Hemoglobin $\geqslant 90$ g/L
   d) Serum creatinine $\leqslant$ 1.5 X upper limit of normal (ULN).
   e) Serum total bilirubin $\leqslant$ 1.5 X ULN (total bilirubin must be < 3 X ULN for subjects with Gilbert's syndrome)
   f) International Normalized Ratio (INR) or Prothrombin Time (PT) $\leqslant$1.5 X ULN
   g) Activated Partial Thromboplastin Time (aPTT) $\leqslant$1.5 X ULN
   h) Aspartate transaminase (AST) and alanine aminotransferase (ALT) $\leqslant$ 2.5 X ULN, or AST and ALT $\leqslant$ 5 X ULN for subjects with liver metastases or HCC
9. Female subjects are eligible to enter and participate in the study if they are of:
   a) Non-childbearing potential (ie, physiologically incapable of becoming pregnant), including any female who
      - Has had a hysterectomy
      - Has had a bilateral oophorectomy
      - Has had a bilateral tubal ligation or is post-menopausal (total cessation of menses

for ⩾1 year)

b) Childbearing potential:
   - 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 (see Appendix 5), and have a negative urine or serum pregnancy test within 7 days of the first dose of study drug

10. Non-sterile males 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 (see Appendix 5)

5.2 Exclusion Criteria

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

1. History of severe hypersensitivity reactions to other monoclonal antibodies
2. Prior malignancy active within the previous 2 years except for tumor under investigation in this trial, cured or 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.
3. Prior therapies targeting programmed cell death-1 (PD-1) or PD-L1
4. Active brain or leptomeningeal metastases. Subjects with brain metastases are permitted if they are asymptomatic, eg, diagnosed incidentally at screening by brain imaging, or subjects with previously treated brain metastases that are asymptomatic at screening, radiographically stable and not requiring steroid medications for at least 4 weeks prior to the first administration of study treatment
5. Subjects with active autoimmune diseases or history of autoimmune diseases or immunodeficiency that may relapse should be excluded. Subjects with following diseases are allowed to be enrolled for further screening: type I diabetes, hypothyroidism managed with hormone replacement therapy only, skin diseases not requiring systemic treatment (such as vitiligo, psoriasis or hair loss), or diseases not expected to recur in the absence of external triggering factors
6. Subjects should be excluded if they have a condition requiring systemic treatment with either corticosteroids (prednisone > 10 mg/day or equivalents) or other immunosuppressive medications within 14 days of study drug administration

   Note: Adrenal replacement doses of prednisone ⩽ 10 mg/day or equivalents are permitted in the absence of active autoimmune disease; subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption); a brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted
7. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
8. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy, including tuberculosis infection, etc. Antiviral therapy is permitted for subjects with HCC
9. With uncontrollable pleural effusion, pericardial effusion or ascites requiring repeated drainage.
10. Significant cardiovascular diseases, such as heart failure of New York Heart Association cardiac disease Class II or greater, myocardial infarction within the previous 3 months, unstable arrhythmias or unstable angina

Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate

11. With history of alcohol or drug abuse or dependence
12. With known history of human immunodeficiency virus (HIV)
13. Subjects with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers with HBV DNA ⩾ 500 IU/mL (2500 copies/mL), or active hepatitis C should be excluded. Subjects with inactive hepatitis B virus surface antigen (HBsAg) carriers, active HBV infection with sustained viral suppression (HBV DNA < 500 IU/mL [2500 copies/mL]), and subjects whose hepatitis C has been cured can be enrolled
14. Underlying medical conditions that, in the investigator's opinion, will make an administration of study treatment hazardous or obscure the interpretation of toxicity determination or adverse events; or insufficient compliance during the study according to investigator's judgment
15. Prior chemotherapy, radiotherapy, immunotherapy or any investigational therapies (including Chinese herbal medicine and Chinese patent medicines) used to control cancer must have been completed at least 2 weeks before the 1st study drug administration, and all adverse events have returned to either baseline or grade 0~1 according to CTCAE version 4.03 (except for alopecia)
16. Use of any live or attenuated vaccines within 4 weeks (28 days) prior to initiation of study therapy
17. Major surgical procedure (Grade 3 or 4) within the past 4 weeks (28 days) prior to study drug administration
18. Prior allogeneic or solid organ transplantation

5.3 Other Eligibility Criteria Consideration

To assess any potential impact of subject eligibility on safety, the investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the investigational product being used in this study.

For Exclusion Criterion 14, the investigators can discuss with medical monitors from the sponsor to decide whether or not to exclude subjects.

During the screening period, repeated measurements may be performed for ineligible laboratory tests, based on the investigator's judgment and with the consent of the sponsor's medical monitor. For subjects that repeat their tests based on clinical status, the most up-to-date measurements should be evaluated during the screening period. If the most recent measurement is still unacceptable, the subject can be recorded as failed screening.

Screening failed patients may be re-screened under special circumstances, depending on the investigator's decision and with the consent of the sponsor's medical monitor.

5.4 Subject Restrictions

The following restrictions may affect subject participation in this study:

- The investigator must be informed as soon as possible about any medications taken from the time of screening until the subject is discharged from the study

5.5 Subject Discontinuation (Dropout/Withdrawal)

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the sponsor if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the sponsor immediately when a subject/patient has been discontinued/withdrawn due to an adverse experience. When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements in Section 8.4.

The reason for discontinuation of the subject will be recorded in the electronic case report form (eCRF). These reasons include:

- Withdrawal of consent by the subject,
- Termination of the study by the sponsor,
- Pregnancy,
- Any AE that compromises the subject to participate in the study,
- The investigator or sponsor determines it is in the best interest of the subject,
- Intercurrent illness,
- Confirmed progression of disease at any time during the study (refer to Section 8.6.1).
- Need of prohibited medication,
- Lack of compliance with the study and/or study procedures (eg, administration instructions, study visits),
- Significant deviation from the protocol by the investigator without the consent of the sponsor.

5.6 Medical Treatment of Subject after Treatment Period Completion

Patients who complete their Treatment Period (2 years after their first dose) may continue to receive therapy. The investigator will evaluate whether continued treatment is in the best interest of the patient based on clinical benefit and potential risk. Continuation of therapy beyond 2 years must be explicitly approved by the sponsor, and will be contingent on the continued availability of BGB-A317 drug product. The assessment and procedures schedule will remain the same as during the Treatment Period.

5.7 Reinitiation of Study Therapy for Subjects in Follow-up Period

If patients have confirmed CR, PR, or SD after 2 years of BGB-A317, the treatment can be stopped if the patient wishes. The decision should be based on the investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. A treatment-interruption informed consent form

must be signed by patients who stop treatment. The investigator should notify the sponsor that treatment will be stopped prior to the event. In such a case, the study assessments and procedures will be performed every 12 weeks (in conjunction with repeat radiographic imaging, as described in Section 8.6) rather than every cycle. If a patient has evidence of PD within 1 year of treatment interruption, the investigator can consider restarting BGB-A317 therapy after discussion with the sponsor, contingent on the continued availability of BGB-A317 drug product.

5.8 End of Study

The end of study is defined as the date when the last patient completes the study. A patient's individual completion is defined as the date of one of the following, whichever occurs first:

- Completion of study treatment at 2 years since first dose
- Completion of the Safety Follow-up Visit if study treatment is discontinued
- Condition that precludes completion of the Safety Follow-up Visit, including death, withdrawal of consent, or loss to follow-up

5.9 Drug Supply for Patients Who are Still on Treatment at End of Study

After the study finishes, the sponsor will continue to supply BGB-A317 to patients, free of charge, through either an extension study or an independent drug supply project to be determined by the sponsor. These programs will be contingent on the continued availability of drug product. Patients will receive BGB-A317 until intolerable toxicity, disease progression, withdrawal of informed consent, or unfavorable risk/benefit assessment at the discretion of the investigator.

All assessments defined as part of the End of Treatment Visit must be performed before a patient may enter one of these programs.

6. STUDY TREATMENTS

6.1 Description of Investigational Product

BGB-A317 is a monoclonal antibody drug which is 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. See Section 6.5 below for handling and product storage conditions. The drugs of 3 manufacturing processes and scales that are used in this clinical trial are tabulated as below in Table 5.

Table 5. Product information about three manufacturing processes and scales

Name of trial drug	Process/Scale	Utility in This Clinical Trial
500L-OMP	CMC-OMP/500L	Used for Phase I-dose verification study and Phase II study
500L-FMP	CMC-FMP/500L	Used for Phase I-PK sub-study
2000L-FMP	CMC-FMP/2000L	Used for Phase I-Dose verification study, PK sub-study and Phase II study

Abbreviations: CMC, Chemistry, Manufacturing and Control; FMP, final manufacturing process; OMP, Original Manufacturing Process; PK, pharmacokinetics.

6.2 Product Preparation and Administration

BGB-A317 will be administered by IV infusion using a volumetric pump through an intravenous line containing a sterile, non-pyrogenic, low-protein binding 0.2 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, subjects who receive the first two infusions of BGB-A317 must be observed for 2 hours after infusion, in an area with resuscitation equipment and emergency agents.

BGB-A317 will be diluted to a concentration between 1 mg/mL to 10 mg/mL in sterile normal saline (0.9% sodium chloride) as described below. The first infusion should be administered over 60 min; if well-tolerated, the second infusion should be administered over 30 min. Do not co-administrate other drugs through the same infusion line.

1. Slowly swirl solution in the vial. Allow up to 5 minutes for bubbles to clear. Do not shake the vial.
2. Visually inspect the solution for particulate matter and discoloration prior to preparation. The antibody drug solution is a clear to slightly opalescent, colorless to slightly yellow solution.
3. Isolate the vial for investigation if extraneous insoluble particles other than translucent to white proteinaceous particles are observed.

4. Aseptically withdraw the required volume from the vial(s) of BGB-A317 into a syringe, and transfer into an IV bag (if multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on). Visually inspect the used vial, and isolate the vial for investigation if extraneous insoluble particles other than translucent to white proteinaceous particles are observed.

5. Please use the following example to guide study drug preparation. The total dose to be administered will be diluted to a total volume of no more than 100 mL in sterile normal saline (0.9% sodium chloride).

   Prepare BGB-A317 solution for infusion per the example provided below:

   200 mg dose:

Drug needed for dose preparation:	200 mg/10 mg/mL = 20 mL
0.9% sodium chloride needed for dilution:	50 mL – 20 mL = 30 mL
Target final concentration:	200 mg/50 mL = 4 mg/mL

   The study center can adjust preparation process according to common practice in consultation with sponsor.

6. Mix diluted solution by gentle inversion for several times.

7. Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be isolated for investigation (according to the instruction in Section 6.5) and documented on the Drug Accountability Log.

8. Record the time when BGB-A317 was prepared on the IV bag label.

9. Attach the IV bag containing the BGB-A317 solution to the infusion set, 0.2 μm in-line or add-on filter, and infusion pump.

10. At the end of the infusion period, flush the line with a sufficient quantity of normal saline.

For management of toxicity refer to Section 4.3.

6.3 Treatment Assignment

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number after signing the informed consent. Subject numbers will be assigned in chronological order starting with the lowest number. Once a subject number has been assigned to a subject, it cannot be reassigned to any other subject.

6.4 Packaging and Labelling

BGB-A317 was aseptically filled in 20R glass vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial contains 10 mL of the drug solution. The vials were packaged in carton box.

The primary labeling on the vials contain following information: protocol number, concentration and quantity of BGB-A317, batch number, expiry date, storage instructions, and administration instructions. The contents of the label will be in accordance with all applicable regulatory requirements.

6.5 Handling and Storage

The investigational product will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures.

Investigational product must be distributed or given according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or give investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with investigational product-specific requirements. The Investigational product must be kept at 2-8^{o}C. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

6.6 Product Accountability

The investigator is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain investigational product accountability records throughout the course of the study. Such person(s) will document the amount of investigational product received from the sponsor, the amount supplied and/or administered to and returned by subjects, if applicable. If the drug that subject received during treatment is changed from a manufacturing process to another, the changes will be recorded, including date and manufacturing processes and scales, etc.

After completion of the study, all unused BGB-A317 will be inventoried on site after receiving written sponsor approval, and returned to the sponsor's supplier for uniform destruction.

6.7 Assessment of Compliance

On all visits to the study center, subjects will be questioned regarding compliance with study instructions.

6.8 Investigational Product Overdose

Overdose is defined as: the subject has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%. Subjects with a suspected overdose should be managed with

appropriate supportive therapy as determined by the investigator in consultation with the Medical Monitor. Any adverse effects occurring as a result of an overdose should be reported to the medical monitor as well as being included in standard AE reporting.

6.9 Medical Care of Subjects after the End of Trial

After a subject has completed the trial or has withdrawn early, conventional treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice, and depending on the subject's individual medical needs.

6.10 Occupational Safety

The investigational product is not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from the sponsor.

7. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1 Concomitant Medication(s)/Treatment(s)

The best supportive care is permitted in the course of the study. Bone metastatic subjects who had been previously treated with bisphosphonates and receptor activators of nuclear factor KappaB ligands (RANK-L) inhibitors are allowed to continue their use during the trial. Subjects with central nervous system metastasis are allowed to undergo Whole brain radiotherapy and / or stereotactic brain radiotherapy, but the extra-cranial lesions of the subjects are required to be relatively stable. All concomitant medication will be recorded on the eCRF including all prescription, over-the-counter, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date will also be included on the eCRF.

All concomitant medications received within 30 days before the screening visit (Visit 1) and within 30 days after the end of treatment should be recorded.

The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medication.

7.2 Prohibited Medications

Subjects may receive other medications that the investigator deems to be medically necessary, except for non-protocol specified chemotherapy, radiotherapy, immunotherapy, anti-neoplastic biological therapy, anti-neoplastic Chinese patent medicine or Chinese herbal medicine, or investigational agents other than BGB-A317 (Palliative radiotherapy for the purpose of alleviating urgent symptoms on non-target lesions is permitted, for example palliative radiotherapy for the purpose of alleviating pain at bone lesions). Subjects who in the assessment by the investigator require the use of any of the aforementioned treatments for clinical treatment should be discontinued from the study.

Subjects with active autoimmune disease or history of autoimmune disease that might recur, who require immune suppressive treatment including systemic corticosteroids, should be excluded; these include but are not limited to subjects with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis, systemic lupus erythematosus, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's, ulcerative colitis, hepatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, or anti-phospholipid syndrome.

Subjects are prohibited from receiving live vaccines 28 days prior to the first dose and until 60 days after the last dose. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

Section 5.2 of the protocol (Exclusion Criteria) describes other medications which are prohibited in this study.

7.2.1 Other Drugs to be Used in the Study

H1 blockers (diphenhydramine 50 mg IV, or equivalent) and acetaminophen (500 to 650 mg oral or IV) may be used 30 to 60 minutes prior to each BGB-A317 infusion to prevent infusion-related reactions. Systemic corticosteroids used for the control of infusion-related reactions or irAEs must be gradually tapered for at least 1 month before the next study drug administration, and the tapered dose after tapering should not be immunosuppressive (prednisone or equivalents $\leqslant$ 10 mg/day). The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

Patients with inactive HBsAg carriers, treated and stable hepatitis B (HBV DNA less than 500 IU/mL or 2500 copies/mL) and cured hepatitis C patients were allowed to be enrolled in the trial. Patients with positive HbsAg at screening and those enrolled in Arm 11 will be further tested for HBV DNA. In terms of definition and treatment of hepatitis B, please refer to the guidelines for the prevention and treatment of chronic hepatitis B (Hou J, 2017). Subjects with positive screening HBV DNA should be regularly monitored for HBV DNA during the trial. Patients with antiviral treatment indications should continue to receive antiviral treatment during the trial.

7.2.2 Other Study Considerations

The following nondrug therapies must not be administered during the study (within 28 days before the start of study treatment):

- Major surgery (excluding prior diagnostic biopsy).
- Herbal remedies with immunostimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).
- Subjects should not abuse alcohol or other drugs during the study.

7.3 Special Precautions

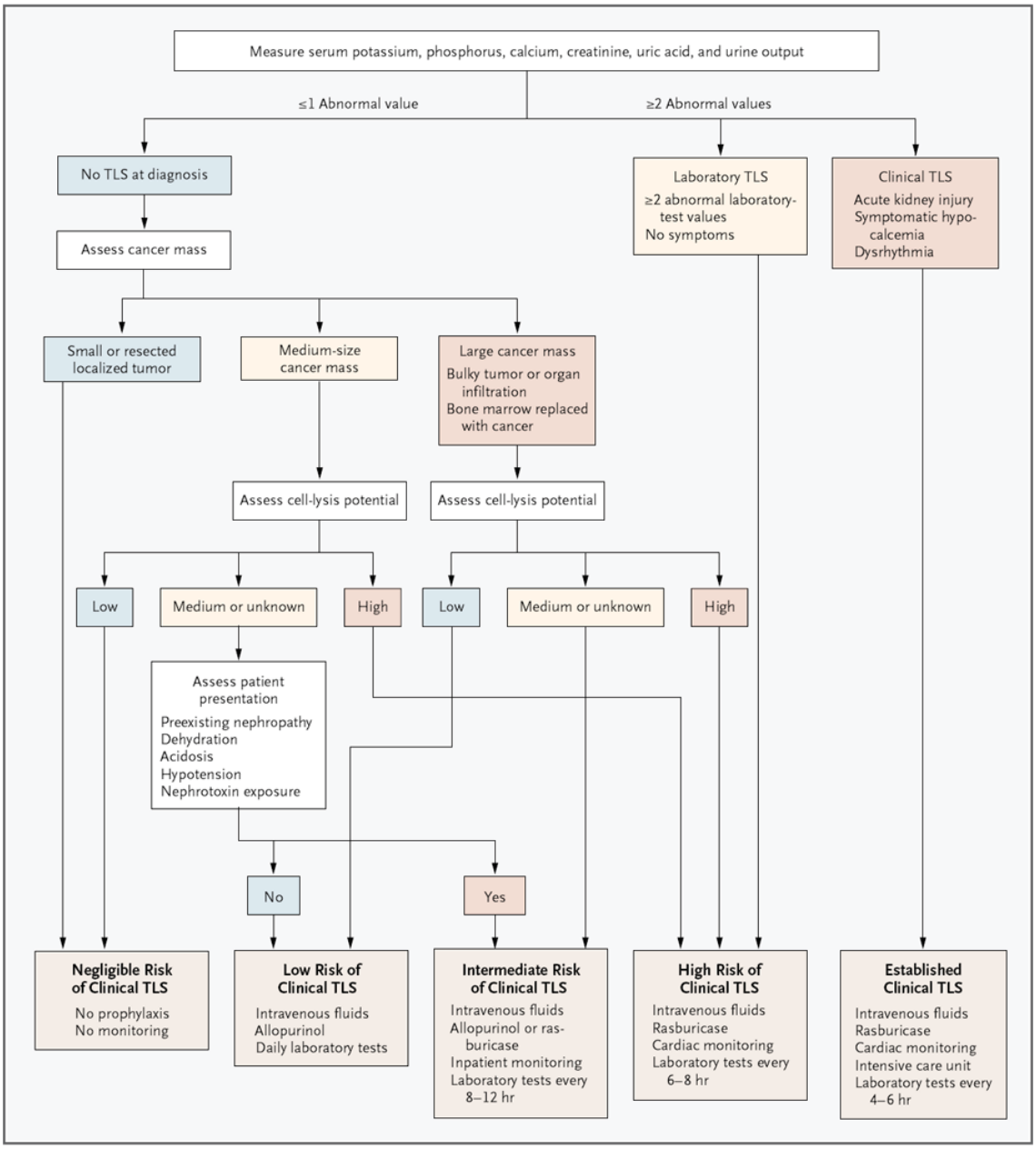
As a routine precaution, subjects who receive the first two infusions of BGB-A317 must be observed for 2 hours after infusion, in an area with resuscitation equipment and emergency agents.

Infusion of BGB-A317 will be discontinued in case of Grade 3 or 4 hypersensitivity, inflammatory response, or infusion-related reactions. Tumor lysis syndrome, the treatment recommendations for infusion-related reactions and severe hypersensitivity reactions according to the NCI-CTCAE are outlined in Sections 7.3.1, 7.3.2 and 7.3.3, respectively.

7.3.1 Tumor Lysis Syndrome

A potential risk of tumor lysis syndrome exists since BGB-A317 can induce cytotoxicity. As published by Howard et al (Howard SC, 2011), once tumor lysis syndrome occurs, subjects should be treated as per the local guidelines and the management algorithm (Figure 1).

Figure 1. Assessment and Initial Management of Tumor Lysis Syndrome.



7.3.2 Infusion-Related Reaction

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

epinephrine, corticosteroids, IV antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modification for symptoms of infusion-related reactions due to BGB-A317 is presented in Table 6.

Table 6. Treatment Modification for Symptoms of Infusion-Related Reactions Due to BGB-A317

NCI-CTCAE Grade	Treatment Modification for BGB-A317
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ⩽ 24 hrs	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions 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 - severe Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 - life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.

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

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 (⩾ 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-related reaction: Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an anti-histamine (eg, diphenhydramine or equivalent), anti-pyretic (eg, paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, 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-related reaction.

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

7.3.3 Severe Hypersensitivity Reactions and Flu-Like Symptoms

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

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

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

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (ie, 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 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. SAFETY, PHARMACOKINETIC, PHARMACODYNAMIC, AND OTHER ASSESSMENTS

A signed, written informed consent must be obtained prior to screening assessments and before any study specific assessments are initiated. The Phase I study specific assessments and procedures are shown in Table 1. The pharmacokinetic sampling time points for dose verification study of Phase I are presented in Table 2. The pharmacokinetic sampling time points for PK sub-study of Phase I are presented in Table 3. The Phase II study specific assessments and procedures are shown in Table 4.

8.1 Screening and Pre-screening

Screening evaluations will be performed within 28 days prior to randomization. Patients who agree to participate will sign the informed consent form (ICF) prior to undergoing any screening procedure. Patients who are suspected or known to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer should take a pulmonary function tests. Screening evaluations may be repeated as needed within the screening period; the investigator is required to assess patient eligibility according to the latest screening assessment results.

In Phase II of this study, tumor samples and/or blood samples should be collected during pre-screening period (≤ 8 weeks prior to screening period) from subjects to be enrolled in Arm 8 when their MSI/MMR-mutation status is unknown. Tests of MSI- or MMR-mutation status of collected samples will be conducted at the central laboratory designated by the sponsor (see Section 8.9):

Following actions will be taken during the process of collecting tumor samples and blood samples for pre-screening:

- Written informed consent forms for pre-screening should be obtained from subjects or subjects' legal representatives
- During pre-screening period, apart from tumor-mutation status, demographic data, medical history and other information will also be collected
- As required by the Lab Manual, tumor samples and blood samples will be prepared and shipped to the central laboratory designated by the sponsor for mutation analysis
- Record SAE directly related to the pre-screening procedures (ie, collection of tumor samples and blood samples). Do not record AE or unrelated SAE, unless such recording is mandatorily required by local regulations

8.2 Demographic and Baseline Assessments

Demographic data will include date of birth, race, height (in cm), and body weight (in kg). For height and weight measurements, the subject will be allowed to wear indoor daytime clothing with no shoes. This data will be captured in the eCRF and database.

Having given consent, subjects will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the inclusion and exclusion criteria listed in

Section 5.1 and Section 5.2. Fresh tumor biopsy samples need to be collected within 42 days prior to the first dosing if subjects have no archival tumor tissue samples. Other screening assessments need to be completed within 28 days prior to the first dose of the investigational product. Related assessments completed within 3 days of administration can be used as Day 1 assessments as indicated in Table 1 and Table 4. The Phase I and Phase II screening assessments will include:

- Baseline demographics
- Medical history including diagnosis, date of first diagnosis, histology, prior anti-neoplastic therapy, and current sites of disease
- Concurrent medications
- Disease assessments within past 4 weeks
- Vital signs
- Physical examinations
- Evaluation of AEs
- ECOG performance status
- Electrocardiogram (ECG)
- Echocardiography (Phase I)
- Ultrasonic echocardiography
- Laboratory tests: hematology, serum chemistry, urinalysis, coagulation (at screening, at the Safety Follow-Up Visit, and during the study when clinically indicated). Refer to Appendix 4 for the list of specific laboratory assessments
- Pregnancy test (for women with childbearing potential only, at screening and during the study when clinically indicated)
- Collection of archival tumor samples (if archival tumor tissue samples are not available, subjects should provide fresh tumor biopsy samples, as detailed in Section 8.9)
- Thyroid function
- HbsAg, HbcAb, hepatitis C virus (HCV) antibody
- Enhanced computed tomography/magnetic resonance imaging (CT/MRI) scan

- Pulmonary function testing which may including but is not limited to spirometry and assessment of diffusion capacity (For patients who are suspected or known to have serious/severe respiratory condition or exhibit significant respiratory symptoms unrelated to underlying cancer)
- For subjects to be enrolled in Arm 2 or Arm 3 in Phase II, PD-L1 detection should be performed, and subjects with non-squamous carcinoma of unknown EGFR mutations should also receive EGFR mutation detection (Refer to Section 8.9)

The above-mentioned data will be captured in the source documents. Any results falling outside the normal range will be repeated at the discretion of the investigator.

Refer to Appendix 4 for the amount of blood samples required at the local study center's laboratory. The final amount of blood samples depends on the standard of the local study center's laboratory. Refer to the Lab Manual for the amount of blood samples required at the central laboratory designated by the sponsor.

All medical history and prior medication should be recorded in the eCRF during screening period. The treatment history of primary diagnosis, including prior systemic treatment, radiation therapy and surgical treatment should all be recorded in the eCRF. The response date and progression date of prior treatment should be recorded. Radiographic studies performed prior to study entry may be collected for review by the investigator. Complete medication history for 30 days prior to the screening visit needs to be reported.

8.3 Assessments During Treatment

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 1 and Table 4.

8.3.1 Laboratory Evaluation

During the study, laboratory assessments should be performed at the local study center's laboratory, including serum chemistry, hematology, coagulation, urinalysis, and thyroid function at the time points specified in Table 1 and Table 4. Subject treatment and overall treatment decisions will be based on the data from study center laboratory. Laboratory assessments need not be repeated on Cycle 1 Day 1 if these assessments were completed for screening within 3 days of the first administration. Required laboratory assessments are listed in Appendix 4.

In the event of neutropenia (ANC $<1000/mm^3$), thrombocytopenia (platelets $<50000/mm^3$), or Grade 3 serum chemistry abnormalities (except some asymptomatic abnormalities), the relevant assessments will be conducted every other day until toxicity resolves to $\leqslant$Grade 2. If warranted, additional testing can also be done, or the relevant tests done more frequently in accordance with institutional guidelines. All subjects who have any Grade 3 or Grade 4 laboratory abnormalities at withdrawal from the study must be followed up until they have returned to Grade 1 or Grade 2 or being stable, unless these are not likely to improve due to the underlying disease.

Urine samples shall be collected over 24 h for total protein analysis if urinary protein dipstick test result is ⩾ 2+ and considered as clinically significant by the investigator in performing urinalysis. The study drug will be suspended if urine protein is > 2 g /24 h, until it drops to ⩽ 2 g /24 h. If urine protein is is2 g /24 h, further clinical evaluation and/or more frequent examinations will be performed when clinically indicated.

8.3.2 Physical Examination, Vital Signs and ECOG Score

A complete physical examination, vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature, and respiratory rate), weight examination and ECOG score will be performed at the time points specified in Table 1 and Table 4.

For the first infusion of BGB-A317, the subject's vital signs should be determined within 60 minutes before the infusion, and during and 30 minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion and if clinical indicated, during and 30 minutes after the infusion. Subjects will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. Refer to Section 7.3.2 regarding precautionary monitoring of subject post-infusion of BGB-A317.

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. Subjects must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is >150/100 mmHg in a subject without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a subject with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

8.3.3 Electrocardiogram

After the subjects have a rest for at least 5 minutes, electrocardiograms will be obtained at the time points specified in Table 1 and Table 4.

Significant QT interval corrected for heart rate (QTc) prolongation will be defined as an interval ⩾500 msec or an interval which increases by ⩾60 msec over baseline. Either of these conditions should be documented on two or more ECG tracings separated by at least 5 minutes. The ECG tracing should be examined and a manual measurement by a trained physician should be performed to assess the accuracy of the equipment being used.

If a subject has significant QTc prolongation:

- The subject will be withdrawn from the investigational product administration if the investigator and/or the medical monitor determine the subject is at risk
- The subject will be monitored, treated appropriately, and closely followed (ECGs at least three times per week) until the QT and QTc interval return to within 30 msec of baseline

- The medical monitor will be consulted prior to administering further doses or re-challenging

8.3.4 Ultrasonic Echocardiography

Echocardiographic parameters of left ventricular ejection and cardiac function will be measured during the screening period of phase I and when clinically indicated.

8.3.5 Pulmonary function testing

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

8.3.6 Computed Tomography and Magnetic Resonance Imaging

Radiographic assessment of the tumor response state should be conducted during screening period, treating period and at the time of disease progression. The frequency of assessment during treatment is approximately every 9 weeks within the first 12 months, and every 12 weeks thereafter.

Sites of enhanced CT scan/MRI (oral or intravenous contrast product) at baseline include chest, abdomen and pelvis at least. If subjects are contraindicated to contrast agents, MRI may also be used. According to the characteristics of the disease, enhanced CT/MRI scan of bones, head, neck, and extremities may be performed. Bone lesions may be evaluated with technetium 99 m bone scan.

For each subject, throughout the study period, radiographic methods and operating procedures for measurable or non-measurable lesions should be consistent with those used at baseline. All target and non-target lesions identified during the screening period should be adequately evaluated during treatment and at the End of Treatment visit. If disease progression is suspected, the investigator can decide to perform unscheduled tumor evaluation at any time.

Subjects who stop treatment prior to confirmed progressive disease (PD) will continue to undergo radiographic examination for tumor response assessments during the study until unequivocal PD is documented or the subject starts new anticancer therapies or subject withdraws consent from the trial, whichever occurs first. This imaging schedule will be maintained and will never be adjusted regardless of any intermediate unscheduled scans. Subjects who withdraw from the study for clinical or symptomatic deterioration before objective documentation of PD should undergo appropriate imaging to confirm PD. Every effort will be made to confirm a clinical diagnosis of PD by imaging.

Lesions that are expected to require palliative radiotherapy while in the study should not be included as target lesions, but should be listed as non-target lesions.

8.3.7 Adverse Events

Refer to Section 10 for AE collection.

8.4 Safety Assessments

Vital signs, weight, physical examinations, ECOG performance status, ECGs and laboratory safety tests (eg, hematology, serum chemistry, urinalysis, coagulation, anti-BGB-A317 antibodies, thyroid function, viral antigen reactions) will be obtained and assessed at designated time intervals throughout the study (see Table 1 and Table 4). Special attention will be given to irAEs (eg, gut, skin, lung, liver, kidney, endocrine organs, others).

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.03. Characterization of toxicities will include severity, duration, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance status, ECGs, and vital signs.

The continuous safety evaluation will be performed by the sponsor and investigators. An SMC will be established to determine the dose levels and dose regimens to be administered during dose verification study, and to recommend RP2D based on the safety and tolerability of BGB-A317. Meanwhile, the SMC will also decide whether or not to increase unscheduled doses for trial. Details of the safety monitoring process will be specified in an SMC charter.

8.5 Follow-up Assessments

All subjects should return to study sites for final assessment at least 30 days, approximately, after end of study treatment or until initiation of a new anti-cancer treatment, whichever occurs first. Assessments to be performed are listed in Table 1 and Table 4.

Subjects who are discontinued from the study due to an intolerable drug related adverse event will be followed until the resolution of the AE to Grade 0-1 or keeping stable.

Following completion of the treatment and safety follow-up periods, all subjects will be followed for survival status. Subjects will have their survival status assessed approximately every 3 months by either a telephone or in-person contact until subject death or termination by the sponsor. No other data (eg, subsequent therapies, performance status, etc) beyond survival will be collected during these calls/visits.

8.6 Efficacy Assessments

This study includes preliminary assessments of efficacy.

Disease assessment by radiographic imaging (enhanced CT or MRI) will be performed and recorded at screening within 28 days before enrollment and while on study approximately every 9 weeks during first 12 months and approximately every 12 weeks thereafter according to the RECIST V1.1 Guidelines as shown in Appendix 6.

After the first confirmation of CR or PR, an imaging test will be performed at 4 weeks later or at the next scheduled time point to confirm the response.

8.6.1 Treatment after Disease Progression

There is evidence that a minority of subjects having received immune therapy with anti-PD1 therapies such as BGB-A317 may still develop pseudo-progression despite initial documentation of progressive disease by RECIST Version 1.1. Pseudo-progression may occur due to immune cell infiltration and other mechanisms resulting in apparent increase of existing tumor masses or appearance of new tumor lesions (Wolchok JD, 2009). If subjects with pseudo-progression continue receiving treatment, they may exhibit a PR at a later time point. It is the responsibility of the investigator to determine if the subject should be considered for treatment beyond progression due to clinical benefit according to the principles described below. This decision should be considered carefully so as to permit subjects who are likely to be benefiting to continue treatment while at the same time preventing prolongation of a futile therapy in subjects who may not be benefitting. If conditions permit, biopsy of lesions with false progression may also be considered to guide further treatment decisions. Any decisions to continue treatment beyond initial progression must be discussed with the medical monitor and documented in the study records.

Subjects with documented progression in tumor burden or with the appearance of new lesions in the absence of significant clinical deterioration (decline in performance status and/or laboratory values) are permitted to continue with treatment until confirmation of disease progression with repeat imaging at least 4 weeks later or at the next regularly scheduled imaging time point. The next imaging to confirm disease progression must not exceed 12 weeks from initial documentation of disease progression.

In addition, subjects must meet the following criteria:

- Absence of clinical symptoms and signs of disease progression (including worsening laboratory values)
- Stable ECOG performance status
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, 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.

In rare cases, subjects with unequivocal radiographical disease progression at repeat imaging may be allowed to continue to be treated if in investigator's opinion subjects are benefitting from the treatment. Prior consultation with the sponsor is required.

8.6.2 Efficacy Endpoints

Efficacy endpoint measures include:

- The ORR, defined as the percentage of subjects in the study whose best overall response was either CR or PR, as assessed by investigators based on RECIST Version 1.1
- The PFS and DCR (CR + PR + SD) as assessed by RECIST Version 1.1; and CBR (CR + PR + durable SD [SD ⩾24 weeks])
- Duration of response (DOR) for responders (CR or PR) and duration of SD

In addition to RECIST Version 1.1, Gynecological Cancer Intergroup (GCIG) criteria (Rustin GJ, 2011) may also be used to evaluate response in patients with ovarian cancer enrolled in the study

8.7 Pharmacokinetics

Blood will be collected to characterize the PK profile of BGB-A317. PK analyses of dose verification study of Phase I and that of Phase II will include but is not limited to $AUC_{0\text{-}21\ day}$, C_{max} and T_{max}, C_{trough}, $t_{1/2}$, Cl and V_z. Phase I PK sub-study aims to assess the PK of the products derived from two manufacturing processes and scales, which includes but is not limited to AUC_{∞}, $AUC_{0\text{-}21\ day}$, C_{max} after the first dosing, as well as other pharmacokinetic parameters such as T_{max}, C_{trough}, $t_{1/2}$, Cl and V_z. This will be used for descriptive statistics rather than statistic influence.

Details concerning handling of PK serum samples, including labeling and shipping instructions will be provided in the Lab Manual. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Blood samples for PK analysis will be collected according to the Lab Manual and serum will be separated, and immediately frozen and shipped per Lab Manual. Samples will be shipped to the sponsor-designated central laboratory where all samples will be analyzed for serum BGB-A317 concentration.

8.7.1 Phase I

For subjects in the dose verification stage, blood-sampling time points are shown in Table 2. For subjects in PK sub-study stage, blood-sampling time points are shown in Table 3.

Unscheduled blood samples may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples should be obtained, when possible, for analysis of serum BGB-A317 in the event of a DLT or any grade 3 or above irAE (refer to Appendix 3). The investigator must record the time the blood samples obtained and the time of the previous administration in the eCRF.

Should a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction as decided by the investigator in consultation with the sponsor.

8.7.2 Phase II

For subjects attending in the indication-expansion study, blood-sampling time points are shown in Table 4.

Unscheduled blood samples may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related. Blood samples should be obtained, when possible, for analysis of serum BGB-A317 in the event of any grade 3 or above irAE(refer to Appendix 3). The investigator must record the time the blood samples obtained and the time of the previous administration in the eCRF.

8.8 Anti-Drug Antibody

Immunogenic responses to BGB-A317 will be assessed to determine occurrence of anti-BGB-A317 antibodies. Blood-sampling time points for subjects both in the dose verification study and in the PK sub-study of Phase I are shown in Table 1, and those in Phase II are shown in Table 4. Samples will be processed according to the Lab Manual and shipped to the central laboratory designated by the sponsor for analysis using a validated method.

8.9 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

8.10 Appropriateness of Measurements

All efficacy, safety and PK assessments used in this study are standard, namely, widely used and generally recognized as reliable, accurate, and relevant.

9. QUALITY CONTROL AND QUALITY ASSURANCE

According to the good clinical practices (GCP) guidelines (CPMP/ICH/135/95, 1996), the sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures.

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s).
- Local study center's laboratories for laboratory measurements and ECGs.
- Study center initiation visit.
- Early study center visits post-enrollment.
- Routine study center monitoring.
- Ongoing study center communication and training.
- Data management quality control checks.
- Continuous data acquisition and cleaning.
- Internal review of data.
- Quality control check of the final clinical study report.

In addition, the sponsor and/or the CRO clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, PK laboratories, local study center's laboratory, vendors, clinical database, and the final clinical study reports. When audits are conducted, access must be authorized for all study-related documents including medical history and concomitant medication documentation to authorized sponsor's representatives and regulatory authorities.

9.1 Monitoring

In accordance with applicable regulations, GCP, and sponsor procedures, the sponsor has engaged the services of a CRO to perform all monitoring functions within this clinical study. Monitors will work in accordance with the sponsor or CRO standard operating procedures (SOPs) and have the same rights and responsibilities as monitors from the sponsor's organization. Monitors will establish and maintain regular contact between the investigator and the sponsor.

During these contacts, the monitor will:

- Check the procedures of the study.
- Check study data collected.
- Conduct source document verification.
- Identify any issues and address their resolution.
- Ensure that data are authentic, accurate, and complete.
- Ensure that safety and rights of subjects are being protected.
- Ensure that the study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

9.2 Data Management/Coding

An electronic data management system will be applied in this study. Data administrators will construct electronic Case Report Form (eCRF) according to the study protocol and medical records.

- Authority distribution: the data administrator will create respective accounts and grant different authorities to different identities such as data entry personnel, investigators, clinical monitors and others. Each site is able to view its own contents. Data entry personnel have authorities of data entering, data modifying and query resolving; investigators have authorities of query modifying, query reviewing, query resolving and auditing; Monitors have authorities of query reviewing and query initiating; and data administrators have authorities of query reviewing, query initiating and data locking.

- Data entry: clinical investigators or investigator's designated data entry staffs (Clinical Coordinators) should timely and accurately enter the data from source documents into eCRF.

- Query initiating & resolving: monitors and data administrators initiate queries via eCRF, data entry staff or investigators answer queries and modify incorrect data. Query initiation may be repeated if necessary. All records are documented in eCRF.

- Data modification & reviewing: data entry staffs or investigators are able to modify the data after verification. Reasons of data modifications should be filled out in eCRF. Investigators have the authority of review all final data.

- Data locking & export: all data review as accurate will be eventually locked by data administrators. No further modification is allowed after data locking unless signed permission is obtained from the sponsor, investigators, entry personnel, monitors and data administrators. All final data is transferred into the database designated by data administrators, and will be analyzed by statisticians.

- Coding: Adverse events, concomitant diseases and prior medical history will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1 or above, and concomitant medications will be encoded using the WHO Drug Dictionary.

9.3 Quality Assurance Audit

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.

10. 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.

10.1 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 tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions. AEs observed with anti-PD-1 therapy are presented in Section 10.7.1.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested workup procedures, study drug management and treatment for suspected irAEs are provided in Appendix 3.

10.2 General Plan to Manage Safety Concerns

10.2.1 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 considered. Specifically, patients at risk for study-emergent active autoimmune diseases or history of autoimmune diseases that may relapse, and patients who have received a live viral vaccine within 28 days before randomization, are excluded from the study.

10.2.2 Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events, defined and graded according to NCI-CTCAE v4.03. Patients will be assessed for safety (including laboratory values) according to the schedule in Table 1 and Table 4. 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 the 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 study (AE from the time of the first dose and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study treatment or until the initiation of another anticancer therapy, whichever occurs first. At the end of treatment, ongoing adverse events considered related to study treatment will be followed until the event has resolved to baseline or ⩽ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study treatment or participation is not the cause of the adverse event.

All irAEs will be recorded until up to 90 days after the last dose of BGB-A317, regardless of whether the patient starts a new anticancer therapy. All drug-related SAEs will be recorded by the investigator after treatment discontinuation until patient death, withdrawal of consent, or loss to follow up, whichever occurs first.

Investigators are instructed to report all events (including AEs and pregnancy-related AEs). In addition, the 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.

10.3 Adverse Events

10.3.1 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.

10.3.2 Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE 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 10.6.2.1.

10.3.3 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 IB 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.

Investigators must also systematically assess the causal relationship of AEs to study drug (including any other non-study drugs, radiation therapy, etc) using the following definitions:

- Definitely related: There is clear evidence to suggest a causal relationship to the study drug, and there is reasonable temporal relationship; the occurrence of AE is definitely attributed to the pharmacological effect of study treatment.
- Probably related: There is a reasonable temporal relationship to suggest a causal relationship to the study drug; the occurrence of AE could not be explained by the patient's medical history, concurrent medical condition, or other signs or symptoms.
- Possibly related: There is some evidence to suggest a causal relationship to the study drug (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 such as the patient's clinical condition or other concomitant AEs.
- Possibly unrelated: There is little evidence to suggest a causal relationship to the study drug. There is another reasonable explanation for the AE such as disease or other drugs.
- Unrelated: An AE will be considered "not related" to the use of the study drug if any of the following criteria are met:
    - An unreasonable temporal relationship between administration of the drug and the onset of the AE (eg, the AE occurred either before or too long after administration of the drug for it to be considered drug-related);
    - A causal relationship between the drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident);
    - A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE).

The causality for cases that were assessed using the 5-point scale will be mapped to 2-point scale during aggregate safety data analysis according to the BeiGene latest mapping rule.

10.3.4 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 10.6.2.1.

10.3.5 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count (CBC), coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator. In general, these are the laboratory test abnormalities that are associated with clinical signs or symptoms, or require active medical intervention, or lead to dose interruption or discontinuation, or require close observation, more frequent follow-up assessments, or further diagnostic investigation.

10.4 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

10.5 Suspected Unexpected Serious Adverse Reaction

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

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

10.6.1 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. Immune-related adverse events (serious or non-serious) should be reported until 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.

10.6.2 Reporting Serious Adverse Events

10.6.2.1 Prompt Reporting of Serious Adverse Events

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

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

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

Abbreviation: SAE, serious adverse event.

10.6.2.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 10.6.2.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

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

The investigator must always provide an assessment of causality for each SAE as described in Section 10.3.3.

The sponsor will provide contact information for SAE receipt.

10.6.2.3 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 10.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the institutional review board/independent ethics committee (IRB/IEC).

All SUSARs (as defined in Section 10.5), will be submitted to all applicable regulatory authorities and investigators for BGB-A317 studies.

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

10.6.3 Eliciting Adverse Events

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

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

10.6.4 Recording Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

10.6.5 Disease Progression

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

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

10.6.6 Deaths

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

10.6.7 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 adverse event, 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.

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

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

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

- BGB-A317 Investigator's Brochure

10.7 Assessing and Recording Immune-Related Adverse Event

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-related (see Section 10.7.1) should be classified as irAEs and identified as such in the eCRF AE page until Day 90, after treatment discontinuation.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 3.

An extensive list of potential irAEs appears in Section 10.7.1, Table 8. All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 3.

10.7.1 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.

A list of potential irAEs is shown below in Table 8. All conditions similar to those listed should be evaluated in patients receiving BGB-A317 to determine whether they are immune-related.

Recommendation for diagnostic evaluation and management of irAEs is based on the European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Brahmer et al., 2018, Haanen et al., 2017). Common immune-related toxicities are detailed in Appendix 3. For any adverse events not included in Appendix 3, please refer to the ASCO Clinical

Practice Guideline (Brahmer et al., 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

Table 8. Immune-Related Adverse Events

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; 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.

Dose modification and management for irAEs are detailed in Appendix 3.

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

11. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Sample Size Considerations

The sample size at Phase I dose-verification study will depend on the number of dose levels assessed and the occurrence of dose-limiting toxicity (DLT) at each dose level. The safety of to-be-assessed doses will determine whether it is necessary to evaluate additional doses with corresponding sample sizes. It is expected that about 20 subjects will be enrolled.

In Phase I PK sub-study, total 48 subjects (24 per arm) are planned to be enrolled to receive treatment of BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP).

In Phase II dose-expansion study, approximately 220 subjects will be enrolled for preliminary efficacy and safety of BGB-A317 monotherapy. The statistical basis for the number of subjects enrolled into each group in Phase II will be detailed in the Statistical Plan.

11.2 General Considerations for Data Analysis

Data will be listed and summarized using Version SAS® 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) according to sponsor agreed reporting standards, where applicable. Complete details will be documented in the reporting and 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 event rates may also be provided if applicable for specific time to event variables

Efficacy and safety data will be statistically collected by stage and indication unless otherwise specified. Further description of the statistical methods and analyses will be provided in the statistical analysis plan.

11.2.1 Analysis Sets

Safety analysis set: including all subjects who have received (or begun to receive) BGB-A317.

PK analysis set; including all subjects who have valid data of BGB-A317 PK parameters after receiving treatment.

Efficacy analysis set: including all subjects who have received any dose of BGB-A317 and had measurable disease per investigator according to RECIST v1.1 at baseline and post-baseline.

All assessable data of other parameters will also be included in the summaries.

Detailed statistical methods will be thoroughly described in the Statistical Plan.

11.2.2 Study Analysis

This study protocol includes 3 categories of analyses.

The first analysis will be performed after the dose-limiting toxicity (DLT) assessments among the Phase I subjects has completed, which will focus on evaluation of the safety, tolerability and PK analysis of BGB-A317.

The second analysis will be performed for PK sub-study in Phase I, assessing PK characteristics, safety and anti-tumor activity in patients receiving BGB-A317 of two manufacturing processes and scales (500L-FMP and 2000L-FMP).

RP2D and the method of drug administration for the Phase II study will be determined according to the results of the first analysis. The third analysis will be carried out after the completion of the entire study, including the safety, tolerability, pharmacokinetics and efficacy of BGB-A317. This study will end if all subjects experience disease progression, intolerable toxicity, death, withdraw from the study or complete the whole 24-month treatment.

All these three categories of analytical results will be included in the clinical study report.

11.3 Efficacy Analyses

Efficacy is not a primary objective of Phase I stage of this study. Objective response rate is a primary endpoint of Phase II stage. There is no formal statistical testing for this endpoint, which will serve as a descriptive endpoint.

Response based on investigators' judgment will be collected in the screening period and while on study approximately every 9 weeks in the first 12 months and approximately 12 weeks thereafter in the simple form of four categories: PD, SD, CR, and PR (according to RECIST Version 1.1). Listing of the data will be provided. If necessary, a summary of data by category will be provided.

Objective Response

The number and proportion of subjects who achieve objective tumor response (CR or PR) or SD will be summarized. Objective response rate will be determined along with 95% confidence interval.

PFS

PFS is defined as the time from the date of first study dose to disease progression or death (whichever occurs first).

Kaplan-Meier methodology will be used to estimate median PFS and 95% confidence interval. Kaplan-Meier curves will be constructed to provide a visual description of the PFS change with time.

DOR

DOR for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of PD or death for any cause (whichever occurs earlier).

Kaplan-Meier curve will be used to estimate median time and 95% confidence interval for DOR.

DCR

DCR is defined as the proportion of subjects in specific tumor types reaching CR, PR and SD in accordance with RECIST V1.1 criteria. DCR will be statistically counted within the 95% confidence interval by tumor type.

CBR

CBR is defined as the proportion of subjects in specific tumor types reaching CR, PR and persistent SD (SD $\geqslant$ 24 weeks) in accordance with RECIST V1.1 criteria. CBR will be statistically counted within the 95% confidence interval by tumor type.

OS

OS is defined as the time from the date of first study dose to death. Kaplan-Meier curve will be used to estimate OS at different time points.

11.4 Safety Analyses

All subjects who have received (or begun to receive) BGB-A317 will be evaluated for safety. Safety data will be summarized according to dose level in dose verification study of Phase I, two manufacturing processes and scales in PK sub-study of Phase I and tumor types in Phase II, respectively.

11.4.1 Dose-Limiting Toxicity

The number and proportion of subjects experiencing DLTs will be reported by dose level, based on DLT observations during Cycle 1 in the dose verification stage of Phase I. The DLT analysis set will be used for this analysis.

No DLT analysis is conducted in Phase II.

11.4.2 Adverse Event

Adverse events will be coded and grouped using the latest version of MedDRA 16.1 or above. Adverse events and toxicities will be graded according to NCI-CTCAE, Version 4.03 (Common Terminology Criteria Version 4.03, 2010). Analyses will include but may not be restricted to:

- All Adverse Events
- Serious Adverse Events (SAEs)

- AEs related to trial medication
- AEs leading to withdrawal of study treatment
- AEs leading to death

The number and percent of subject will be summarized for various items above. And the number and frequency of these adverse events will be also summarized according to MedDRA System Organ Classes and Preferred Terms.

11.4.3 Laboratory Assessments

Clinical laboratory (eg, hematology, serum chemistry) values to be evaluated will be specified in the Statistical Analysis Plan and collected in the electronic data capture (EDC) system. Collected values may be a subset of all the values obtained in the requested sampling, eg, a CBC with differential may be requested to allow for evaluation of neutrophils only. Analyzed laboratory values that are abnormal will be flagged and identified outside (above or below) the normal range.

11.4.4 Electrocardiogram

Clinically significant abnormalities on ECG should be noted in the EDC and changes from baseline will be summarized and listed.

11.4.5 Vital Signs

Specific vital signs, eg, blood pressure and temperature will be summarized and listed. The change from baseline will also be displayed.

11.4.6 Extent of Exposure

Exposure to BGB-A317 will be calculated for each subject. Overall exposure will also be summarized.

11.4.7 Physical Examination

Physical examination results collected in association with an adverse event will be listed and summarized.

11.5 Pharmacokinetic Analyses

Pharmacokinetic parameters will be derived using standard non-compartmental methods with WinNonlin Professional Version 5.2 or higher (Pharsight Corp., Mountain View, California) or SAS® Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina). Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations.

BGB-A317 PK variables (eg, C_{max}, T_{max}, C_{trough}, AUC, Cl, and V_z) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the PK data. An exploratory analysis of a

potential relationship between dose level, PK variables and clinical safety and anti-tumor activity will be performed as appropriate.

11.6 [redacted]

[redacted]

12. ETHICS

12.1 National Regulations and the Declaration of Helsinki

The implementation of the study must be in accordance with the *Good Clinical Practice (GCP)* based on Declaration of Helsinki and laws & regulations applicable to clinical trial conducting in order to protect subjects to be best extent.

12.2 Informed Consent

Investigators or representatives authorized by investigators must obtain the informed consent form signed by subjects participating in the study, must explain the nature, objectives, potential risks and benefits of the study to subjects, and must inform the subjects that they can withdraw from the study at any time without any restriction. If subjects are not able to sign the informed consent form, subjects' legal representatives must sign the informed consent form instead. If subjects and their legal representatives are not able to read the informed consent form, a third-party witness must be present throughout the entire process of informed consent. After subjects and their legal representatives verbally agree to participate in the study, the witness must sign on the informed consent form, and ensure that the subjects and their legal representatives have been fully explained and have understood the content, and that subjects also have known that they can withdraw from the study at any time without any restriction. Subjects' informed consent can be documented in eCRF. If safety results lead to major changes in risk/benefit assessment, the informed consent form should be reviewed and modified if necessary. All subjects (including those who already started to receive treatments) must be notified of updates and may continue with the study only after signing a new informed consent form.

12.3 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The clinical study protocol and its amendments, IB, informed consent form, subject information related to the study (such as subject recruitment advertisement) as well as other required documents should all be reviewed by the Independent Ethics Committee/Institutional Review Board (IEC/IRB).

The study must be approved by the IEC/IRB before initiation, and the date of the meeting with IEC/IRB and date of approval should be indicated in the approval letter to the investigators.

Any amendment to the protocol must be formally approved or kept on record by the IEC/IRB.

All serious adverse events will be reported to the relevant ethics committees and regulatory agencies in accordance with corresponding regulations.

In the middle of the study, any protocol deviations that may increase the risk of subjects should also be promptly reported to the IEC/IRB by the investigator.

12.4 Protocol Modifications

The modified protocol must be submitted to the Ethics Committee for approval. Prior to the approval, investigators should still follow the original study protocol, unless the modifications can immediately

eliminate potential harm to subjects or only involve changes in study management (eg, change of phone numbers, etc.).

13. PRESERVATION OF STUDY DOCUMENTS, CASE REPORT FORM AND RECORDS

13.1 Study Documents and Document Preservation

Investigators must adequately and accurately record the study process and ensure the study data can be verified. These documents can be divided into two categories—one is investigator documents, and the other is original subject data.

Investigator documents include the protocol and its amendments, case report forms and data query forms, approval from Ethics Committees & regulatory agencies and correspondence with them, samples of informed consent forms, study drug inventory, investigators' resumes and authorization forms, and other required documents and correspondence.

The subject's original documents (key efficacy/safety data to be recorded should be pre-defined) include inpatient/outpatient records, the doctor's medical advice, visit reservation date, original laboratory examination results, ECG, CT slices, positron emission tomography reports/slices, pathology reports and reports of special assessments, signed informed consent forms, consultation records and subject screening and enrollment forms, etc.

Investigators need to keep these documents intact within 5 years after the study is completed, and must contact the sponsor before the destruction of any study document.

If investigators are willing to transfer these study documents to another party or another place, please notify the sponsor in advance.

If investigators cannot guarantee the quality of document preservation in the study centers, investigators and the sponsor can jointly arrange to preserve documents in other places. These documents must be preserved sealed, so that investigators will be able to retrieve them in case of audits by regulatory agencies. If the documents will be in use, copies can be preserved at different places.

13.2 Original Documents and Data

When eCRF is illegible or when errors occur in the middle of data transfer, investigators should provide the study documents or original data in medical records upon request of the sponsor. In the cases of specific queries, queries from regulatory agencies and/or request during inspections, complete study records should be accessible on the condition of subjects' privacy being protected.

13.3 Audit and Inspection

The investigator should understand that when the sponsor, a third party designated by the sponsor or the department of drug administration inspects the study, they should be able to directly access the

original documents in the study, and that the data in the eCRF should be directly derived from the original data.

13.4 Case Report Form

The Principal investigator or other designated investigators must complete and sign the eCRF of each enrolled subject and subjects who have failed to complete the study (even including subjects who have failed the screening). If a subject withdraws from the study, the reason of withdrawal should be recorded in the eCRF. If a subject withdraws from the study due to treatment-related adverse events, the outcome should be recorded as clearly as possible.

Investigators should complete eCRF and related forms accurately, completely, clearly and timely.

13.5 Use and Publication of Study Data

13.5.1 Use of Study Data

All study data related to BGB-A317, such as patent applications, dosage forms, production processes and scales, basic research and other information, if not published, should be deemed confidential.

The data obtained in this study will also be considered as confidential information. BeiGene (Shanghai) Co., Ltd. will publicize the data to other clinical researchers, the China National Medical Products Administration or other government agencies at an appropriate time. In order to ensure the integrity of data analysis in this clinical study, investigators have obligation to provide complete study results and data to the sponsor.

Investigators must ensure that subjects' privacy is not disclosed to unauthorized third parties. eCRFs and other documents submitted to the sponsor must not contain the subjects' names that should be replaced with identification codes used for distinction. Investigators may keep enrollment forms containing subjects' identification codes, names and addresses. Informed consent forms and other documents should be preserved strictly confidentially and should not be submitted to the sponsor.

13.5.2 Publication

Study results may be published on core journals. The principal investigator who has major contribution to the study implementation & management and staffs who have made great contribution to study design, explanation or analysis can put names on publications.

BeiGene (Shanghai) Co., Ltd. guarantees that before publishing any result of this study, articles will be provided to investigators for review. Accordingly, investigators should obtain consent from the sponsor before submitting any academic paper or abstract. Investigators have the right to publish results of this study, as long as requirements of confidential data protection are met.

14. REFERENCES

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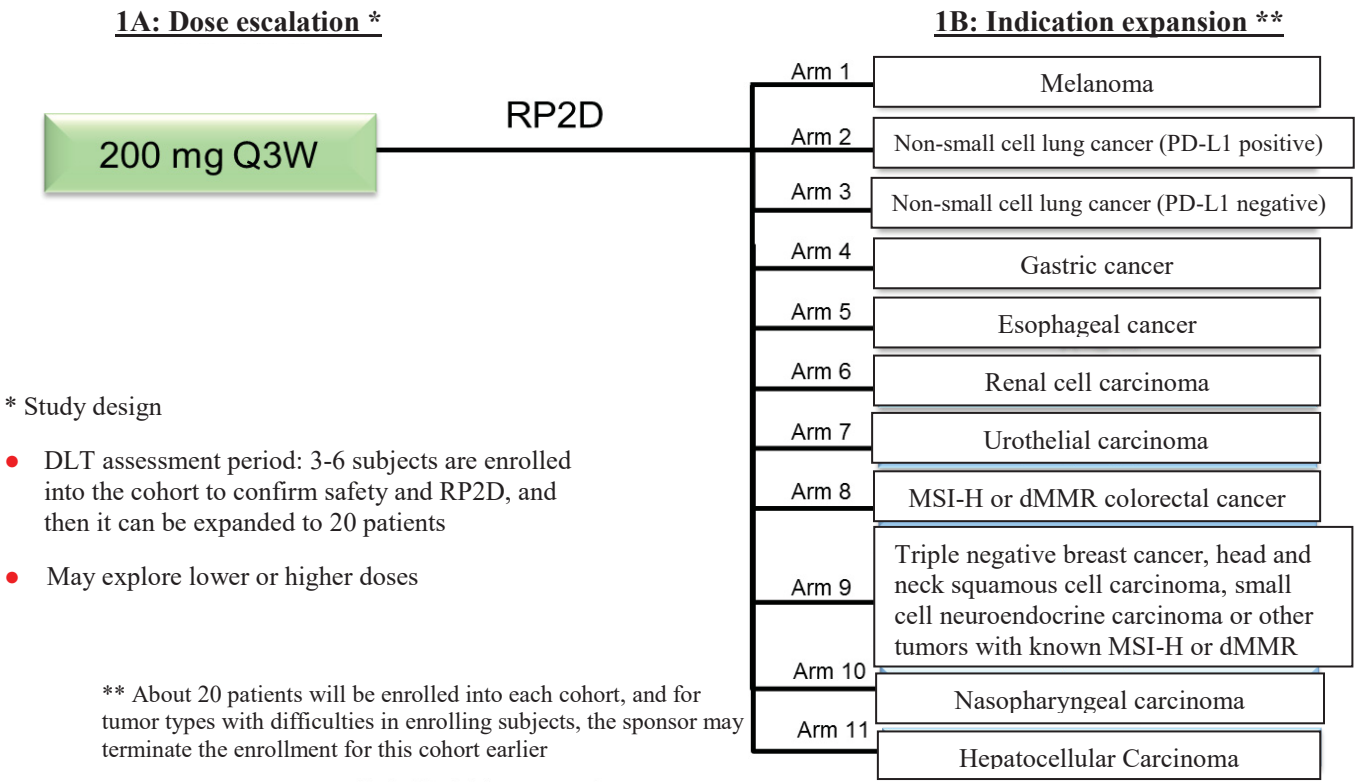
15. APPENDICES

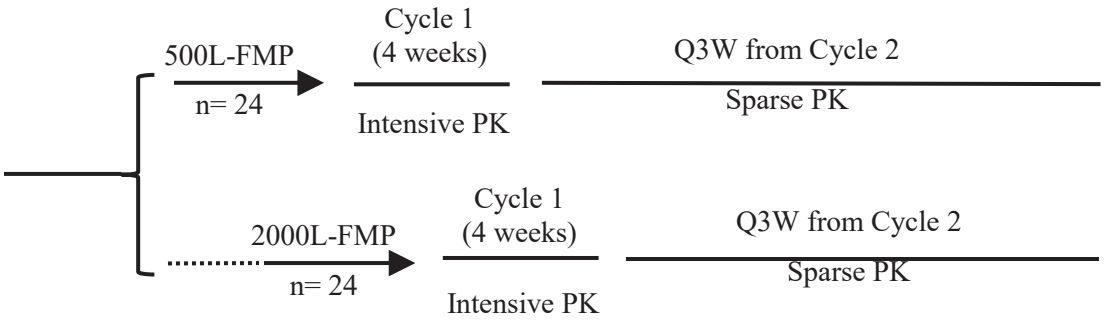
APPENDIX 1. FLOW CHARTS

Test Design



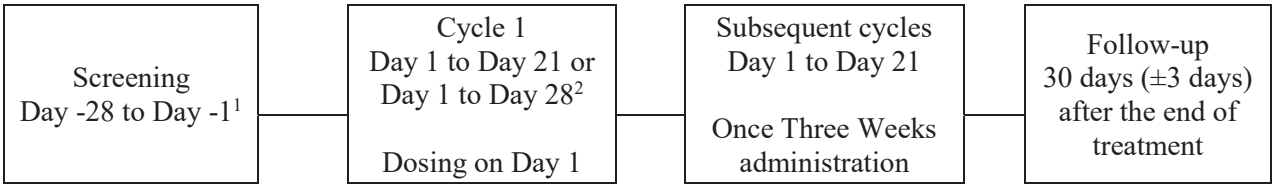
Abbreviations: MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient.

Phase I – Pharmacokinectics (PK) sub-study



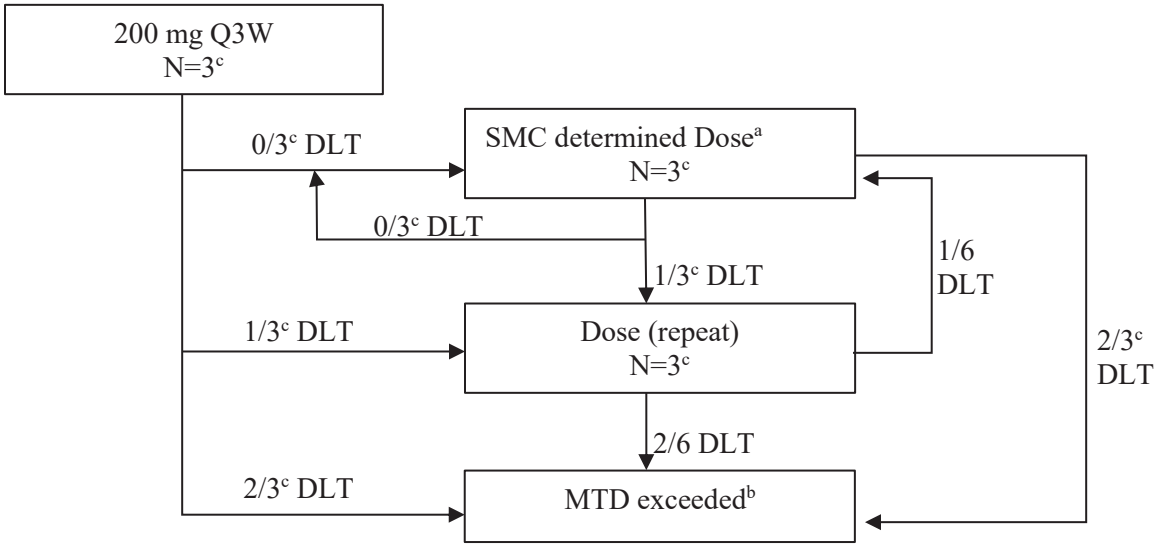
Abbreviation: FMP = Final Manufacturing Process; PK = pharmacokinetics; Q3W = once every three weeks

Flow chart for Phase I



1. Fresh tumor biopsy samples need to be collected within 42 days prior to the first dose if subjects have no archival tumor tissue samples. Other screening assessments need to be completed within 28 days prior to the first dose of the study drug.
2. The duration of the first cycle for the first 20 subjects will be 21 days, and DLT will be conducted in this period; the duration of the first cycle for the rest 48 subjects will be 28 days, which will be performed for the PK analyses of the products derived from two manufacturing processes and scales (500L-FMP vs 2000L-FMP),

Dose Verification for Phase I



Abbreviations: DLT: dose-limiting toxicity; MTD: maximum tolerated dose; SMC: Safety Monitoring Committee.

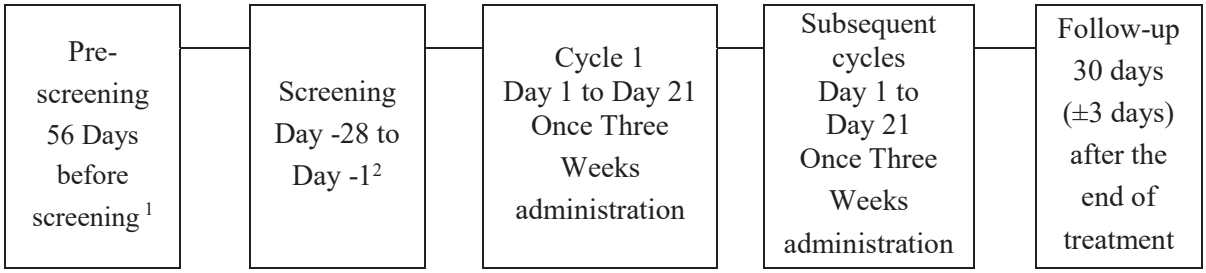
[a] If none (0) of the subjects in the cohort experience a DLT by the end of Cycle 1, the study will proceed to Phase II, as determined by the SMC. If one (1) out of six (6) subjects experience a DLT by the end of Cycle 1, whether or not proceeding to Phase II will be determined by SMC.

[b] No additional subjects will be treated at a given dose level if two (2) or more of the subjects in a cohort develop a DLT in Cycle 1. In this instance the MTD is considered to have been exceeded and as noted above, the MTD will be considered to be the dose level below this level or an intermediate dose level that has been evaluated and has not exceeded the MTD.

[c] Additional subject(s), up to a maximum of six (6) subjects in total, will be enrolled if more than three (3) subjects have been screened and are eligible for the cohort. The DLT assessment and dose-escalation scheme will follow the rules stipulated in the modified 3 + 3 dose escalation scheme. For example, three (3)

additional subjects will be enrolled if a DLT is observed in one (1) of three (3) subjects; additional two (2) subjects will be enrolled if a DLT is observed in one (1) of four (4) subjects; and additional one (1) subject will be enrolled if a DLT is observed in one (1) of five (5) subjects. No additional subjects are required if a DLT is observed in one (1) of six (6) subjects.

Flow chart for Phase II



1. Tumor samples and blood samples should be collected for detecting MSI or MMR mutation status during pre-screening period ⩽ 8 weeks prior to screening period from subjects to be enrolled in Arm 8 when their biomarkers are unknown.
2. Fresh tumor biopsy samples need to be collected within 42 days prior to the first dosing if subjects have no archival tumor tissue samples. Other screening assessments need to be completed within 28 days prior to the first dose of the study drug.

APPENDIX 2. CHILD-PUGH LIVER FUNCTION CLASSIFICATION

The following data were obtained from the Child-Pugh classification criteria by medical center of University of Washington, with references as follows:

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

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

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

Child-Pugh classification is divided into Grade A (mild: 5 to 6 points), B (moderate: from 7 to 9 points), or C (severe: 10 to 15 points). Child-Pugh classification is determined by clinical and biochemical parameters, please see Table 9 for details.

Table 9. Clinical and biochemical parameters of Child-Pugh classification

	Score of the severity of the anomaly		
Clinical and biochemical parameters	**1**	**2**	**3**
Hepatic encephalopathy (Grade) [a]	0[b]	1[c] or 2[d]	3[e] or 4[f]
Ascites	No	mild	moderate
Total bilirubin (mg/dL)	< 2.0	2.0 to 3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prolonged prothrombin time (seconds) or Activated partial thromboplastin time (APTT) INR[g]	< 4 or < 1.7	4 to 6 or 1.7 to 2.3	> 6 or > 2.3

Abbreviation: INR, International standardization ratio

[a] Trey C, Burns DG, and Saunders SJ. Treatment of hepatic coma cornia by exchange blood transfusion. N Engl J Med. 1996;274(9):473-481.
[b] Grade 0: consciousness, personality, neurological examination and ECG are all in normal condition.
[c] Grade 1: restlessness, sleep disorders, irritability / anxiety, hand tremor, writing disorders, 5CPS waves.
[d] Grade 2: lethargy, time barrier, discomfort, asterixis, ataxia, three-phase slow wave.
[e] Grade 3: drowsiness, coma, orientation disorder, over reflection, stiff, slow wave.
[f] Grade 4: Cannot wake up from coma, no independent personality / behavior, irrational, slow 2-3CPS Delta activity.
[g] Lucey MR, Brown KA, Everson GT, Fung JJ, Gish R, Keeffe EB, et al. Minimal criteria for placement of adults on the liver transplant waiting list. Liver Transl Surg 1997;3(6):628-637.

APPENDIX 3. 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.

Table 1. Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

Immune-related Toxicity	Diagnostic Evaluation Guideline
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.
Dermatology	Consider other causes by conducting a physical examination, consider dermatology referral for skin biopsy.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.

Immune-related Toxicity	Diagnostic Evaluation Guideline
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.
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.
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.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all central nervous system 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.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.

Immune-related Toxicity	Diagnostic Evaluation Guideline
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.
Thyroid Disorders	Scheduled and repeat thyroid function tests (TSH and T4).

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

Treatment of Immune-related Adverse Events

- 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
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.
Colitis/ Diarrhea	**1** Mild symptoms: < 3 liquid stool 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.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	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 1 month. 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 Grade 0-1 and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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.	
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week.	Continue study treatment.
	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 at least 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment, treatment may be resumed when resolved/improved to Grade 0-1 and prednisolone tapered to ⩽ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 2-4 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 1 month.	Hold study treatment until improved to grade 2; reintroduce only after discussion with the study medical monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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		
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to grade 2 or less. Discontinuation is usually not necessary.
Mucositis/ Stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a grade 3 event.	Continue study treatment.

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

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement
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 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to Grade 0-1: 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 1 month.	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.
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 1 month.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 1 month. Consider azathioprine, MMF, cyclosporine if no response	Discontinue study treatment.
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
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 $\leqslant$ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.
	3-4 Severe or life-threatening symptoms Breathless at rest	Initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for Pneumocystis infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
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.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	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 2-4 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. Seek urgent dermatology review.	Discontinue study treatment.
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 0.5-1.5 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.

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 4. CLINICAL LABORATORY ASSESSMENTS AND AMOUNT OF BLOOD SAMPLING

Serum Chemistry	Hematology	Coagulation	Urinalysis
Alkaline phosphatase	Red blood cell (RBC) count	Prothrombin time	Leucocyte count
Alanine aminotransferase	Hematocrit	Partial Thromboplastin Time	Protein
Aspartate aminotransferase	Hemoglobin	International Normalized Ratio	Specific gravity
Albumin	MCH		pH
Total bilirubin	MCHC		RBC
Blood urea nitrogen	MCV		Glucose
Calcium	Platelet counts		Nitrite
Chloride	WBC count with differential		Urobilinogen
Creatine kinase	Neutrophil count		Ketones
Creatine kinase-cardiac muscle isoenzyme (CK-MB)[a]	Lymphocyte count		24 h protein[b]
Creatinine	Monocyte count		
Glucose	Basophil count		
Lactate dehydrogenase	Eosinophil count		
Phosphate			
Potassium			
Total protein			
Sodium			

Abbreviations: CK-MB, creatine kinase cardiac isoenzyme; pH, negative of the logarithm to base 10 of the activity of the (solvated) hydronium ion; RBC, red blood cell; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV mean corpuscular volume; WBC, white blood cell.

[a] In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead.

[b] Urine samples will be collected over 24 h for total protein analysis if urinary protein dipstick test result is $\geqslant$ 2+ in performing urinalysis.

Note: On the basis of not affecting the assessment of drug safety, if the study center cannot perform a certain laboratory assessment, an alternative indicator assessment can be used, which will not be considered as a deviation from the protocol.

Laboratory test	Amount of blood sampling (mL)
Serum biochemistry	5
Hematology	3

Laboratory test	Amount of blood sampling (mL)
Coagulation	3
HBV/HCV	5
Thyroid function	3
Pregnancy test	3

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

APPENDIX 5. CONTRACEPTION GUIDELINES

Contraception Guidelines

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

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

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

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

APPENDIX 6. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1) GUIDELINES

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer 2009; 45:228-247.

1 Inclusion Criteria

Only subjects with measurable tumors at baseline can be enrolled into the trial protocol with objective tumor response rate as the primary endpoint.

2 Definition

Measurable Disease—At least 1 measurable lesion. Must be accurately measured, in at least 1 dimension, ⩾ 10 mm in long axis for a lesion and ⩾ 15 mm in short axis for a lymph node when assessed by CT scan slice thickness of 5 mm; ⩾ 20 mm by chest X-ray (if clearly defined); 10 mm caliper measurement by clinical exam (when superficial). Color photographs with scale should be used to clearly show its size. If evaluation can be achieved through imaging techniques, imaging technique assessment should be preferably selected.

Non-measurable Disease—All other lesions, including small lesions (longest diameter < 10mm or pathological lymph node short axis ⩾ 10 to < 15 mm) and really non-measurable lesions. Lesions that are deemed as really non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly that is not measurable by reproducible imaging techniques.

Exceptions of Measurable Disease: Including bone lesions, cystic lesions and lesions with prior local treatment. Bone scan, positron emission tomography scan, or X-ray plain films cannot be used for measurement of bone lesions, but 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. If non-cystic lesions and cystic lesions coexist, non-cystic lesions are preferred for selection as target lesions. Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be recorded in metric notation, using rulers or calipers. 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.

3 Measurement Methods

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.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested.

CT and MRI are the best currently available and reproducible methods to measure target lesions. Conventional CT and MRI use a continuous ≤10 mm thick layer. Spiral CT uses 5 mm thick layer for continuous reconstruction algorithm. This standard is suitable for thoracic, abdominal and pelvic tumors, while head and neck tumors and extremity tumors usually require special schemes.

Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. CT is preferred.

Ultrasound (US) should not be used as a method of measurement of tumor lesion when the primary endpoint of the trial is objective response evaluation. The method is not readily accepted in clinical practice. This method can be used as an alternative method to clinically measure superficially palpable lymph nodes, subcutaneous lesions and thyroid nodules. US approach can also be used to confirm the complete disappearance of superficial lesions that are usually evaluated by clinical examination.

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response if all tumor lesions disappear. Elevations of tumor markers must be accompanied by visible disease progression to meet the requirements of disease progression.

In a few cases, **cytology and histology** can be used to differentiate between PR and CR (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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.

4 Tumor Response Evaluation

4.1 “Target” and “Non-target” Lesions Recorded at Baseline

- All measurable lesions, up to two lesions in each organ, the sum of up to 5 lesions, and representing all the organs involved as **target lesions**, are recorded and measured at baseline.

- The selection of target lesions should be based on the size (lesions with a maximum diameter) and suitability, so that they can be (by imaging techniques or clinically) accurately and repeatedly measured.

- Calculate the sum of the **longest diameter** (LD) of all target lesions, and report it as baseline sum LD. Use baseline sum LD as a reference value for description of objective tumor.

- All other lesions (or sites of disease) should be used as non-target lesions and reported at baseline. These lesions are not required to be measured, but the presence or absence of each lesion during the entire follow-up period should be recorded.

4.2 Criteria for Response

Criteria for 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 LD.
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.

Criteria for Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/SD:	Persistence of ≥1 non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of ≥1 new lesions and/or unequivocal progression of existing non-target lesions.

*** Although unequivocal progression of "non-target" lesions is an exception, the opinion of the treating doctor should be referred to, and the progression status later should be confirmed.**

4.3 Criteria for Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (the minimum measurements recorded from the start of the treatment should

serve as reference values for PD). The subject's best overall response will generally depend on the completion of two measurements and the confirmation criteria.

When the treatment is required to be discontinued due to overall deterioration of the health status, and there is no objective evidence indicating disease progression, the subject should be reported as "symptomatic deterioration." Objective progression should be recorded as far as possible, even after cessation of the treatment.

In some cases, it is difficult to distinguish residual lesion from normal tissue apart. When the evaluation of complete response depends on this decision, it is advised to study the residual lesion (fine needle extraction/biopsy) to confirm the complete response status.

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

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