BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-001
Study Protocol Title:	Study Protocol Title: A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors
Date:	February 12, 2018
Version:	1.0

SIGNATURE PAGE

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Anti-drug Antibody
ADI	Actual Dose Intensity
AE	Adverse Event
$AUC_{0\text{-}14\ day}$	Area under the plasma concentration-time curve from Day 0 to Day 14
BGB-A317	Code name for Monoclonal Antibody BGB-A317
BMI	Body Mass Index
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
CD	Cluster of Differentiation, such as CD274, CD279, CD3 and etc.
CI	Confidence Interval
C1	Clearance
C_{max}	Maximum Observed Plasma Concentration
CR	Complete Response
CRC	Colorectal Cancer
CRF	Clinical Report Form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Minimum Observed Plasma Concentration
DCR	Disease Cont ol Rate
DLT	Dose-Limiting T xicity
DOR	Dur tion of response
ECG	Electroc rdiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFF	Efficacy Evaluable Set
FDA	Food and Drug Administration
HCC	Hepatocellular Carcinoma
HNSCC	Head and Neck Squamous Cell Carcinoma
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
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease, Pharmacodynamics

PD-1	Programmed Cell Death-1
PD-L1	Program Death Ligand-1, Programed Death Receptor Ligand-1, Programed Death-1 Ligand-1
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time or Preferred Term
Q2W	Once Every Two Weeks
Q3W	Once Every Three Weeks
QTc	QT Interval Corrected for Heart Rate
RBC	Red Blood Cell
RCC	Renal Cell Carcinoma
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phases 2 Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Press re
SD	Stable Disease, St ndard Deviation
SI	System International
SMC	Safety Monit ring Committee
SOC	System Org n Class
$T_{1/2}$	Half life
TEAE	Treatme t-Emergent Adverse Event
TIL	Tumor-infiltrating lymphocytes
V_d	Volume of distribution
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for BGB Protocol A317-001 "A Phase 1A/1B, Open Label, Multiple Dose, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumor Activities of the anti-PD-1 Monoclonal Antibody BGB-A317 in Subjects with Advanced Tumors". The focus of this SAP is for the planned primary, secondary and exploratory analysis specified in protocol version 5.0.

2 STUDY OVERVIEW

This is a two-stage study consisting of a Phase 1A dose escalation and dose-finding component to establish the MTD, if any, and RP2D(s), followed by a Phase 1B component to investigate efficacy in select tumor types and to further evaluate safety and tolerability of BGB-A317 at RP2D(s).

Patients 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 8 weeks or 9 weeks depending on dosing schedules in the first year, then every 12 weeks thereafter.

- *Phase 1A, Part 1*

The Phase 1A, Part 1 component is a multi enter, open-label, multiple-dose, dose escalation, first-in-human study. **Four dose levels are planned: 0.5, 2.0, 5.0 and 10 mg/kg, Q2W (once every two weeks)**. The study will follow a modified 3+3 dose escalation scheme. **At least three (3) patients will be enrolled into each cohort. Additional patient(s), up to a maximum of six (6) patients in total, will be enrolled if more than three (3) have been screened and are eligible for the cohort.** The dose-limiting toxicity (DLT) assessment will be conducted in the first cycle consisting of 28 days. Dose escalation will continue until identification of MTD or 10 mg/kg in the event that a MTD is not identified due to paucity of DLTs. Two (2) or more DLT in a cohort of three (3) to six (6) patients is considered to have exceeded MTD.

Continuous safety evaluation will be performed by the Sponsor, the Coordinating Investigator, and Investigators. A Safety Monitoring Committee (SMC) will be established for the determination of dose levels to be administered and dose regimen during dose escalation based on the data available from the previous dose levels.

The SMC may decide to evaluate an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired. If this approach is taken, up to 6 new patients should be enrolled at the new intermediate dose.

- *Phase 1A, Part 2*

The Phase 1A, Part 2 component will evaluate the safety and PK of two dosing schedules Q2W versus Q3W (once every three weeks) at selected doses that have cleared the DLT period without exceeding MTD (eg, 2 mg/kg or 5 mg/kg, up to 10 mg/kg). 10 to 20 patients per dose schedule will be enrolled to evaluate the safety, the PK and preliminary efficacy. Tumor types to be enrolled include but are not limited to colorectal cancer (CRC), non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), bladder cancer, melanoma and ovarian cancer. Other cancers that are deemed to be likely to benefit from programmed cell death-1 (PD-1) inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor. Q2W and Q3W schedule cohorts for each dose may be evaluated sequentially or in parallel.

To adequately monitor safety of patients enrolled in dosing schedule expansion, when at least 6 patients have been treated at a specific dose and schedule and ≥33% of the patients experienced a DLT during the first 28 days in both Q2W and Q3W schedules, study accrual will be held pending data review by the SMC. BGB-A317 will also be withheld in the event of other serious adverse reactions according to pre-specified criteria. In the event that a MTD is not identified, RP2D and dosing regimen used in the Phase 1B stage will be determined by the SMC and the Sponsor based on the PK, tolerability and preliminary antitumor activities observed in the Phase 1A stage, as well as other available data. Based on the Phase 1A data, more than one dose or dosing regimen may be selected to be evaluated in Phase 1B for safety and preliminary efficacy in select tumor types.

- *Phase 1A, Part 3*

The Phase 1A, Part 3 component will evaluate the safety and PK of BGB-A317 at flat dose (ie 200 mg, Q3W) that do not exceed the exposure of the MTD as determined in the Phase 1A, Part 1 study. Approximately 10 to 20 patients will be enrolled. Tumor types to be enrolled include but not limited to NSCLC, RCC, head and neck squamous cell carcinoma (HNSCC), bladder cancer, melanoma, gastric, oesophageal, Merkel-cell carcinoma and HCC. Other cancers that are deemed to be likely to benefit from PD-1 inhibition based on high mutational load, preclinical or clinical data from other studies may be considered for enrollment subject to discussion with the medical monitor in advance.

The doses selected for the flat dose exploration have been evaluated for DLT and demonstrated as safe in the Phase 1A Part 1 study. Nevertheless, to adequately monitor safety of patients enrolled in flat dose exploration, study accrual at a specific dose level will be held pending data review by the SMC when at least 6 patients have been treated and ≥33% of the patients experienced a DLT during the first cycle consisting of 21 days. A planned formal SMC review of safety data will be performed after all patients have completed the first cycle of treatment, or withdrew due to any reason (progressive disease [PD], adverse event [AE], or death).

This part of the Phase 1A study will be conducted in Australia and/or New Zealand sites only and may be conducted in parallel with a Phase 1B study that evaluates a RP2D selected based on the Phase IA, Part 1 and 2 data as described in protocol Section 2.5.4.

- *Phase 1B*

The Phase 1B stage is a multicenter, open-label, multiple-dose, multiple-arm, indication expansion study. The various arms of the study will investigate RP2D(s) to examine the potential efficacy as well as safety and tolerability of BGB-A317 in cancer patients who failed standard care therapies. The cancer indications may include:

Arm 1. Patients with NSCLC (approximately 50 patients)
Arm 2. Patients with ovarian cancer (approximately 20 patients)
Arm 3. Patients with gastric cancer (approximately 50 patients)
Arm 4. Patients with HCC (approximately 50 patients)
Arm 5. Patients with HNSCC (approximately 20 patients)
Arm 6. Patients with esophageal carcinoma (approximately 50 patients)
Arm 7. Patients with triple negative breast cancer (TNBC) (approximately 20 patients)
Arm 8. Patients with cholangiocarcinoma (approximately 20 patients)
Arm 9. Patients with RCC, bladder cancer, melanoma, Merkel-cell carcinoma, sarcoma, gastrointestinal stromal tumor (GIST), or cutaneo s squamous cell carcinoma (cuSCC). Or any other solid tumors with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), such as CRC or pancreatic cancer (approximately 50 patients)

For Arms 1, 3, 4 and 6, at least 20 patients each will be enrolled from Taiwan or Korea. Enrollment rates will be different for each expansion arm. Individual arms may be closed at the discretion of the Sponsor once the target umber of enrolled patients is reached. Individual arms may also be closed prematurely d e to difficulty in recruitment at the discretion of the Sponsor. Patients will receive BGB-A317 at the RP2D as described in protocol Section 2.5.4. Each treatment cycle will be 21 days in duration. Patients will continue treatment until confirmed disease progression, intolerable toxicity, patient discontinuation/ withdrawal or at the discretion of the Investigator in consultation with Sponsor.

To adequately monitor safety of patients enrolled in the Phase 1B indication expansion, when at least 6 patients have been treated and ≥33% of the patients experienced a DLT during the first 21 days, study accrual will be held pending data review by the SMC.

Tumor response and progression will be assessed by Investigators based on the Response Evaluation Criteria in Solid Tumors (RECIST) version (v) 1.1.

3 STUDY OBJECTIVES

Phase 1A

Primary:

- To assess the safety and tolerability of BGB-A317 in patients with advanced tumors

Secondary:

- To characterize the pharmacokinetics (PK) of BGB-A317
- To determine maximum tolerated dose (MTD), if any, and recommended Phase 2 dose (RP2D) for BGB-A317
- To assess the preliminary anti-tumor activity of BGB-A317
- To assess host immunogenicity to BGB-A317

Exploratory:

- [redacted]

Phase 1B

Primary:

- To assess the anti-tumor activity of BGB-A317 in select tumor types

Secondary:

- To further assess the safety and tolerability of BGB-A317 in patients with advanced tumors.
- To further characterize the PK of BGB-A317

Exploratory:

- [redacted]

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

The primary endpoint of the Phase 1A stage is the following:

> BGB-A317 safety and tolerability: The safety of BGB-A317 will be assessed throughout the study by monitoring adverse events (AEs) per the NCI-CTCAE Version 4.03, physical examination, ophthalmologic examination, electrocardiograms, laboratory measurements and severity of adverse events.

The primary endpoint of the Phase 1B stage is the following:

> ORR (complete response [CR] + partial response [PR]) based on RECIST v 1.1 in patients with select tumor types as evaluated by the investigators.

4.2 SECONDARY ENDPOINTS

The secondary endpoints of the Phase 1A stage of the study are the following:

- Pharmacokinetic evaluations: include but not limited to area under the plasma concentration-time curve from Day 0 to Day 14 (AUC0-14 day), maximum observed plasma concentration (Cmax), time to maximum observed plasma concentration (Tmax), minimum observed plasma concentration (Ctrough), half-life (T½), clearance (Cl), and volume of distribution (Vd).
- The MTD, if any, and RP2D (s) for BGB-A317 will be determined based on safety, tolerability, PK, preliminary efficacy, and other available data.
- Efficacy evaluations: ORR (CR+PR), CR rate, PR rate, stable disease (SD) rate, progression-free survival (PFS), overall survival (OS), and duration of response (DOR) will be determined based on Investigator's tumor assessments per RECIST v 1.1.
- Anti-BGB-A317 antibody: immunogenic responses to BGB-A317 will be assessed to determine incidence of anti-drug antibody (ADA).

The secondary endpoints of the Phase 1B stage of the study are the following:

- PFS; disease control rate (DCR: CR + PR + SD); and clinical benefit rate (CBR: CR or PR or durable SD [SD ≥24 weeks]).
- Safety and tolerability assessment of AEs, serious adverse events (SAEs), physical examination, ophthalmologic exam nation, vital signs, electrocardiograms (ECGs), and laboratory measurements.
- Plasma concentrations of BGB-A3 7 at selected time points.

4.3 EXPLORATORY ENDPOINTS

- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

In Phase 1A, the number of dose levels and schedules examined and the emerging BGB-A317 toxicities will determine the sample size. It is anticipated that approximately 24 patients will be required to establish the RP2D(s) of BGB-A317 when administered as a single agent. In addition, 10 to 20 patients will be enrolled in each of the schedule expansion and flat dose cohort at one or

more dose level (up to 10 mg/kg Q2W or Q3W in schedule expansion cohort; 200 mg Q3W in flat dose cohort) not exceeding MTD to further evaluate safety, tolerability, PK and preliminary efficacy of BGB-A317.

In Phase 1B, approximately 20 to 50 patients for each arm will be evaluated to examine the potential efficacy as well as safety and tolerability of BGB-A317 in select tumor types. One or more arms may be closed early due to difficulty in patient recruitment.

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

Safety Analysis Set (SAF) includes all patients who have received any dose of BGB-A317. It will be the primary population for efficacy and safety analysis. Summary analyses will be conducted by actual received treatment group for phase 1A, and by tumor type for phase 1B.

DLT Analysis Set (DLT) includes all patients who experienced a DLT during Cycle 1 plus patients who received at least 90% of the planned doses of treatment during the DLT observation period (Cycle 1).

Efficacy Evaluable Set (EFF) includes all patients in the SAF with measurable disease at baseline per RECIST v1.1 who had at least one evaluable post-baselin tumor assessment unless discontinued due to clinical disease progression or death within 10 weeks of the first dose date.

PK Analysis Set (PKS) include patients who have received at least the first dose of BGB-A317 and provided PK samples as per protocol following first dosing on Day 1.

PD Analysis Set (PDS) include patients who h ve received at least the first dose of BGB-A317 and have evaluable pharmacodynamic data.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Reference date: Reference date is defined as the date of the first dose of study treatment (Day 1 is the day of the first dose of study treatment) and will appear in every listing where an assessment date or event date appears.

Study day: Study days will be calculated in reference to the date of the first dose of study treatment. For assessments conducted on or after the date of the first dose of study treatment, study day will be calculated as (assessment date – date of first dose of study treatment + 1). For assessments conducted before the date of the first dose of study treatment, study day is calculated as (assessment date – date of first dose of study treatment). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings; Study day and any corresponding durations will be presented based on the imputations specified in Appendix.

Treatment duration: The treatment duration will be calculated as (date of last dose of study treatment – date of first dose of study treatment + 21) for Q3W dose regimens, (date of last dose of study treatment – date of first dose of study treatment + 14) for Q2W.

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the time of first dose date.

All calculations and analyses will be conducted using SAS version 9.2 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with nonmissing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, and range (minimum and maximum)
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3 Handling of Missing Data

Missing data will not be imputed nless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

6.2.4 Adjustment for Covariates

Not applicable.

6.2.5 Multiplicity Adjustment

No multiplicity adjustments will be made.

6.2.6 Data Integrity

Before pre-specified interim or final statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All data should be

complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification should be complete.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Patient Disposition

The number (percentage) of patients with treatment ongoing, discontinued from the treatment/study, and reasons for discontinued from treatment/study will be summarized in the SAF

6.3.2 Protocol Deviations

Protocol deviation criteria will be established; patients with protocol deviations will be identified and documented before the database lock for the interim and primary analyses.

Critical and major protocol deviations will be summarized by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the SAF. Continuous variables include age, BMI (in kg/m^2), body weight (in kg), height (in cm); categorical variables include sex, race, nicotin use status, alcohol consumption and ECOG status.

6.3.4 Disease History

Type of solid tumor, site of curre t tumor solid tumor stage at study entry, histology/cytology, histologic grade and time from ini ial diagnosis to study entry will be summarized using descriptive statistics in the SAF. A listing of disease history will be provided.

6.3.5 Prior Anti-Cancer Drug Therapies and Surgeries

The number of prior anti-cancer drug therapies, prior anti-cancer radiotherapy and prior anti-cancer surgeries will be summarized. Prior anti-cancer drug therapies will be summarized by preferred term.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded using current version of World Health Organization Drug Dictionary (WHO DD) drug codes, and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term.

Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. A listing of prior and concomitant medications will be provided.

6.3.7 Medical History

Medical history will be coded using MedDRA codes of the version currently in effect at BeiGene at the time of databased lock. The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the SAF. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

6.4.1 Primary Efficacy Endpoints

Analysis described here will be applied for both Phase 1A and Phase 1B data, though ORR is not the primary endpoint in Phase 1A setting.

Objective Response Rate (ORR)

The number and proportion of patients who achieved confirmed objective tumor response (CR or PR) as evaluated by investigator according to RECIST v1.1 will be summarized. Patients without postbaseline tumor assessment will be considered as non-responders.

Primary analysis of ORR will be based on SAF. Analysis of ORR will also be conducted in the EFF as a sensitivity analysis.

A two-sided binomial exact 95% confidence inter al (CI) of ORR will be constructed to assess the precision of the point estimate of ORR

6.4.2 Secondary Efficacy Endpoint

Disease Control Rate (DCR)

DCR is defined as the proportion of patients in specific tumor types reaching CR, PR and SD in accordance with RECIST v1.1 criteria. Patients without postbaseline tumor assessment will be considered as failure in DCR.

Clinical Benefit Rate (CBR)

CBR is defined as the proportion of patients in specific tumor types reaching CR, PR and durable SD [SD ≥24 weeks]. SD duration is measured from the start of study treatment until the time that the criteria for progression are met.

Progression Free Survival (PFS)

PFS is defined as the time from the date of first dose of study treatment 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 rate versus time.

The PFS derivation rules in this SAP follow Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)" with minor modification.

Table 1 shows the primary censoring rules for the derivation of PFS using RECIST v1.1 criteria based upon investigator's tumor assessment.

Table 1 Censoring Rules for Analysis of Progression-Free Survival Per RECIST v1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Date of the first dose	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of 1 st adequate radiologic assessment prior to or on date of n w anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,
* Adequate tumor assessment is a radiologic ssessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

The priority of the censoring rules in the primary analysis is as follows:

1. If the patient had PD or death, the following sequence will be applied:
   - If a patient did not have baseline tumor assessment (No. 1), the patient will be censored on date of the first dose of study treatment. However, if the patient died within 70 days (10 weeks) after the first dose date and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
   - If a patient had new anticancer treatment before PD or death (No. 4), the patient will be censored on the date of the last tumor assessment prior to or on the date of new anticancer treatment.
   - Otherwise, if a patient had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.
2. If a patient did not have PD or death, the censoring date will be the earliest censoring date if the patient met multiple censoring criteria (No. 1, No. 3, No. 4).

Clinical PD will be considered as event in a sensitivity analysis.

Overall Survival (OS)

Overall survival is defined as the time from the date of the first dose of study treatment to death. Patients who remained alive at data cutoff or discontinuation of the study (discontinued study due to reasons other than "Death") will be censored at the time of the last date the patient was known to be alive.

Kaplan-Meier curve will be used to estimate OS at different time points.

Duration of Response (DOR)

Duration of response 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). Duration of response analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule.

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

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion. The maximum tumor shrinkage based on target lesion used in the plots will be listed. These analyses will be performed based on RECIST v1.1.

6.4.3 Subgroup Analyses

No subgroup analysis is planned.

6.4.4 Exploratory Endpoints

[redacted]

6.5 SAFETY ANALYSES

All safety analyses will be performed in the SAF. Treatment extent of exposure, Incidence of treatment emergent adverse events, dose limiting toxicities, death, laboratory, vital signs, ECOG Performance Status and ECG will be analyzed; Abnormal values will be flagged.

6.5.1 Extent of Exposure

Descriptive Statistics (n, mean, standard deviation, median, minimum and maximum) will be estimated for continuous variables including total dose in mg, duration of treatment, actual dose intensity, relative dose intensity, number of cycles. Categorical variables include duration of treatment in months, number of cycles received, number of patients with dose modification (dose delay or interruption) and dose delay due to AE.

In addition, frequency of dose delay and frequency of dose interruption will be summarized by categories (0, 1, ≥2).

Actual dose intensity (ADI) per patient (mg/cycle) which is defined as sum of actual dose received divided by duration of treatment and relative dose intensity (RDI) per patient (%) defined as actual dose intensity/planned dose intensity per patient will be summarized.

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

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE v4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the date of the first dose of study treatment through 30 days after the last dose (permanent discontinuation of study treatment) or initiation of new anti-cancer therapy whichever occurs earlier. The TEAE classification also includes irAEs that are recorded up to 90 days after discontinuation from treatment. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

An overview table, including the in idence of and the number of patients with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patient s with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT.

The number (percentage) of patients with treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose interruption will be summarized by SOC and PT.

Patient data listings of all AEs, SAEs, AEs that led to death and AEs that led to treatment discontinuation will be provided.

All deaths and causes of death will be reported, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation.

6.5.3 Laboratory Values

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for hematology, biochemistry, coagulation, and urinalysis values and their changes from baseline will be summarized by visit.

Laboratory results will be summarized using System International (SI) units, as appropriate. For all quantitative parameters listed in Table 2, the actual value and the change from baseline to each post-baseline visit and to the end of treatment will be summarized by visit using descriptive statistics.

Laboratory parameters (Alkaline phosphatase, Alanine aminotransferase, Aspartate etc.) that are graded in NCI CTCAE (v. 4.03) will be summarized by shifts from baseline CTCAE grades to worst post-baseline grades. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions will be summarized separately. Number (percentage) of patients with abnormal postbaseline laboratory values will be summarized.

Table2: Clinical Laboratory Assessments

Serum Chemistry	CBC with Differential	Coagulation	Urinalysis
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Blood urea nitrogen Calcium Creatinine Glucose Lactate dehydrogenase Phosphate Total protein Potassium Sodium	RBC Count Hematocrit Hemoglobin Platelet counts WBC count with differential Neutrophil count Lymphocyte count	Prothrombin time Activated Partial thromboplastin Time International Normalized Ratio	24-hour protein Random urine protein to creatinine ratio

6.5.4 Vital Signs

The change from baseline and Potentially Clinical Significant (PCS) vital signs in blood pressure, pulse rate, weight, temperature in Celsius will be summarized in descriptive statistics.

6.5.5 Physical Examination

A listing of physical examination results will be provided.

6.5.6 Electrocardiograms (ECG)

ECG will be performed at the baseline and multiple time points (refer the time points to the protocol study assessments and procedures schedule) after the start of treatment. Observed and change from baseline in ECG will be summarized.

6.5.7 Eastern Cooperative Oncology Group (ECOG)

A shift table from baseline to worst post-baseline in ECOG performance status will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Refer to a separate PK analysis plan.

6.7 IMMUNOGENIC ANALYSES

Human anti-drug antibodies (ADA) to BGB-A317 will be assessed during the study as defined in the protocol.

ADA attributes:

- Treatment boosted ADA is defined as ADA positive at baseline that was boosted to a 4 fold or higher level following drug administration.
- Treatment-induced ADA is defined as ADA negative at baseline and ADA positive post-baseline.
- **Persistent ADA response** is defined as Treatment-induced ADA detected at 2 or more time points during treatment or follow-up, where the first and last ADA positive samples are separated by 16 weeks or longer; or detected only in the last time point or at a time point less than 16 weeks before a negative last sample.
- **Transient ADA response** is defined as Treatment-induced ADA detected only at 1 time point during treatment or follow-up, excluding last time point; or detected at 2 or more timepoints during treatment or follow-up, where the first and last positive samples (irrespective of any negative samples in between) are separated by less than 16 weeks and the last time point is negative. Transient ADA is a treatment-induced response that is not considered persistent.
- **Neutralizing ADA** is defined as ADA that inhibits or reduces the pharmacological activity.

ADA response endpoints:

- **ADA incidence** is defined as sum of treatment-emergent ADA, which include both treatment-induced and treatment-boosted ADA-positive patients, as a proportion of the ADA evaluable population.
- **ADA prevalence** is defined as proportion of all patients that are ADA positive, including pre-existing ADA, at any time point.

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

6.8 OTHER ANALYSES

PD and biomarker analyses will be summarized separately from the primary analyses, as appropriate.

7 INTERIM ANALYSIS

This is a two-stage study consisting of a Phase 1A stage followed by a Phase 1B stage.

The Phase 1A stage is a multicenter, open-label multiple-dose, dose escalation, first-in-human portion of the study. The Phase 1A, Part 1 component is a multiple-dose, dose escalation to establish the MTD. The Phase 1A, Part 2 component assesses the safety and PK of two dosing schedules Q2W versus Q3W at selected doses. The Phase 1A, Part 3 component determines the safety and PK of BGB-A317 at flat dose that do not exceed the exposure of the MTD as determined in the Phase 1A, Part 1 study

The interim analysis which includes safety, efficacy, and PK for each component will be performed once the Phase 1A stage is completed.

8 CHANGES IN THE PLANNED ANALYSIS

NA

9 REFERENCES

Brookmeyer R, Crowley J. A confidence interval for the median survival time, Biometrics 1982; 38(1): 29-41.

Common Toxicity Criteria Version 4.03. Cancer Therapy Evaluation Program. June 2010.

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; 45:228-47.

Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research (2007). FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007).

International Conference on Harmonization Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). July 1996.

Kaplan E, Meier P. Nonparametric estimation from incomplete observations. Journal of American Statistical Association. 1958;53:457-81.

Greenwood M. "The natural duration of cancer". Reports on Public Health and Medical Patients (London: Her Majesty's Stationery Office). 1926; 33:1-26.

Shankar, G., Arkin, S., Cocea, L. et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. AAPS J (2014) 16: 658.

10 APPENDIX

10.1 IMPUTATION OF MISSING/PARTIALLY MISSING DATES

Missing data will not be imputed unless otherwise specified. The imputation rule for the safety analyses will be used to address the issues with partial dates.

When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment-emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month

If year of the start date is missing, or star date is completely missing, do not impute.

If end date of an adverse event is p rtially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If year of the end date is missing, end date is completely missing, do not impute

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medications:

If start date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.