BeiGene

BGB-A317-203 (NCT03209973)

A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-203
Study Protocol Title:	A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma
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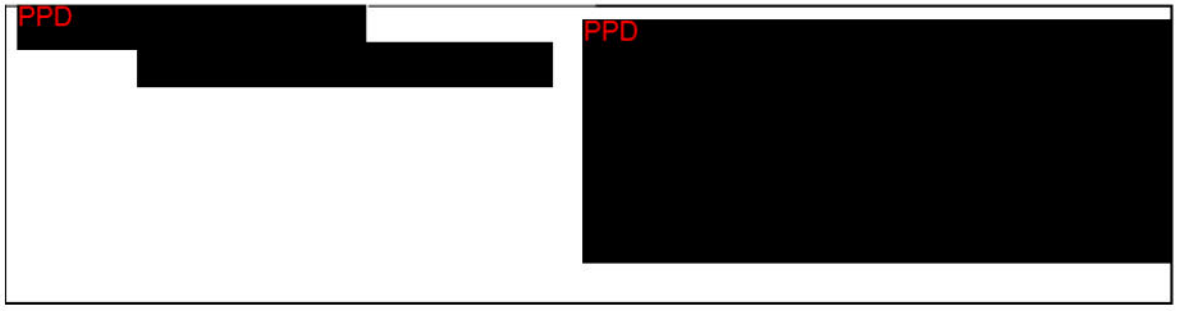

Approval

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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	Area under the concentration-time curve
BOR	Best overall response
Auto-SCT	Autologous stem cell transplant
CA 125	Carcinoma antigen-125
cHL	Classical Hodgkin lymphoma
CI	Confidence interval
[redacted]	[redacted]
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCIG	Gynecologic Cancer Intergroup
IPS	International Prognostic Score
irAE	Immune-related adverse event
IRC	Independent Review Committee
MTD	Maximum tolerated dose
MAD	Maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall response rate
CCI [redacted]	[redacted]
PD	Progressive disease

CCI	[redacted]
PFS	Progression-free survival
PR	Partial response
PS	Performance status
PT	Preferred term
RDI	Relative dose intensity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment-emergent adverse event

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 A317-203 a "A Single Arm, Multicenter, Phase 2 Study of BGB-A317 as Monotherapy in Relapsed or Refractory Classical Hodgkin Lymphoma". The focus of this SAP is for the planned primary, secondary and CCI of the study.

CCI

Reference materials for this statistical plan include the protocol BGB-A317-203 (dated as 13-July-2018). If the protocol is amended or updated then appropriate adjustments to the SAP may be made as necessary. Any changes in the analyses since the finalization of this document will be described and documented in the CSR.

All statistical analyses will be conducted using SAS® Version 9.3 or higher.

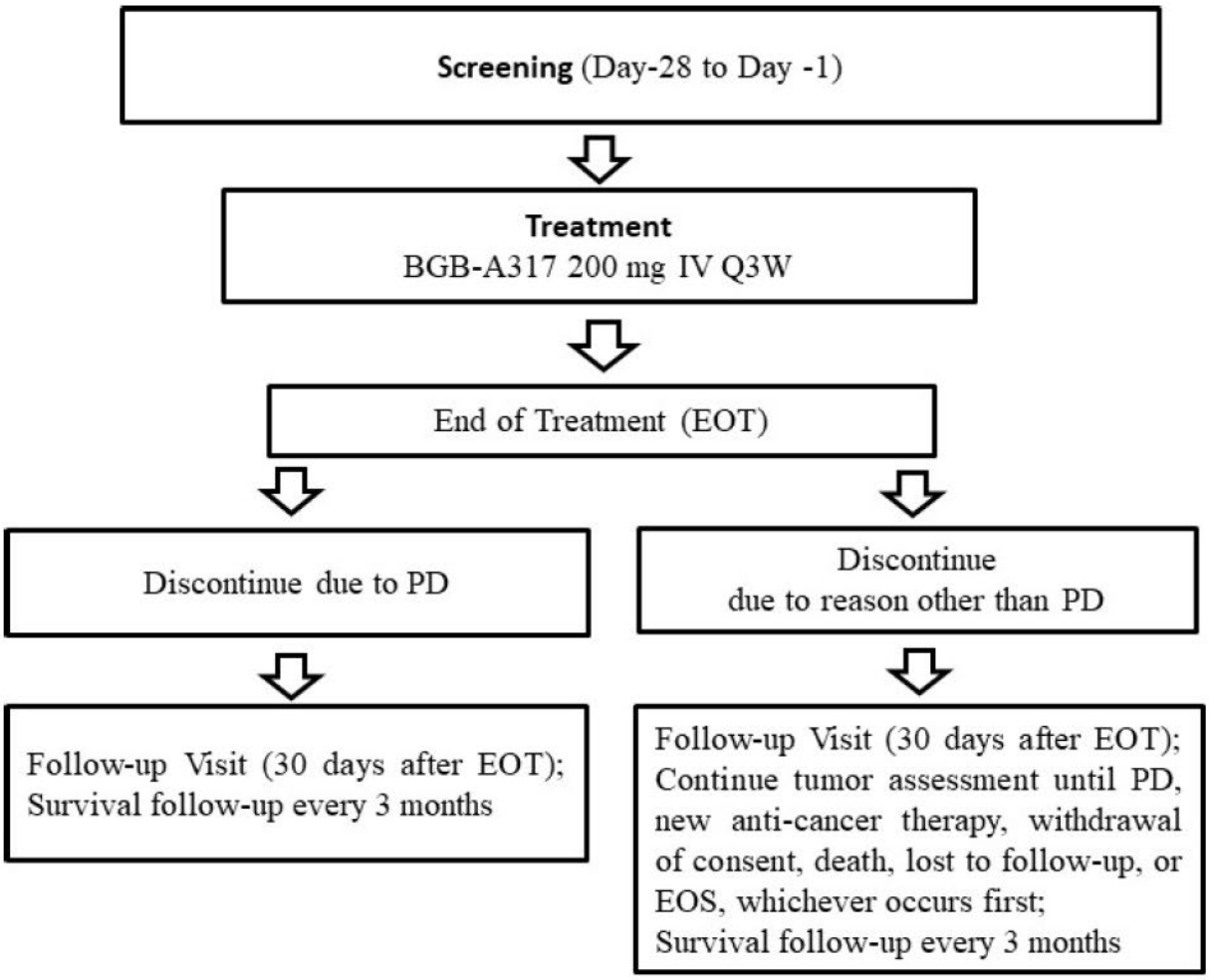
2 STUDY OVERVIEW

This is an open-label, multi-center, single-arm Phase 2 study to evaluate BGB-A317 therapy in adult patients with relapsed or refractory cHL Patients must have either failed to achieve a response or progressed after auto-SCT, or are not candidates for auto-SCT due to chemo-resistant disease, advanced age (≥ 65 years), failure to collect stem cells or unable to perform stem cell collection as assessed by the investigator, or any significant existing medical conditions and have received at least two prior systemic chemotherapy regimens for cHL

Approximately 68 patients will be enrolled onto study to receive BGB-A317 at a dose of 200 mg IV Q3W. Study treatment will continue until PD, unacceptable toxicity, death, or study withdrawal for other reasons.

Study design is depicted in Figure 1.

Figure 1 Study Design



Note: Patients who discontinue treatment for any reason will be asked to return to the clinic for a safety follow-up visit (to occur within 30 days [± 7 days]) after the last study treatment. In addition, telephone contacts with patients should be conducted to assess AEs and concomitant medications (if appropriate, ie, associated with an AE or is a new anti-cancer therapy) at 60 and 90 days (±14 days) after the last dose of BGB-A317. All AEs and SAEs are collected up to 90 days after the last dose of study drug. Beyond 90 days, investigators should continue to report any SAEs that are believed to be related to study drug if they become aware of them.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

To evaluate the efficacy of BGB-A317 assessed by IRC in patients with centrally confirmed relapsed or refractory cHL, as measured by Overall Response Rate (ORR) per the Lugano Classification (Cheson et al, 2014; refer to Appendix 6 in the protocol)

3.2 SECONDARY OBJECTIVES

To evaluate BGB-A317 with respect to:

- Progression-free Survival (PFS) assessed by IRC per the Lugano Classification (Cheson et al, 2014)
- Duration of Response (DOR) assessed by IRC per the Lugano Classification (Cheson et al, 2014)
- Rate of CR assessed by IRC per the Lugano Classification (Cheson et al, 2014)
- Time to Response assessed by IRC per the Lugano Classification (Cheson et al, 2014)
- Safety and tolerability

3.3 CCI

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINT

- Overall Response Rate (ORR) defined as the proportion of patients who achieves a best response of CR or PR, assessed by IRC per the Lugano Classification (Cheson et al, 2014).

4.2 SECONDARY ENDPOINTS

- Progression-free Survival (PFS) defined as the time from the first dose of BGB-A317 to the date of PD or death, whichever occurs first, assessed by IRC per the Lugano Classification.

- Duration of Response (DOR) defined as the time from the date that response criteria is first met to the date that PD is objectively documented or death, whichever occurs first, assessed by IRC per the Lugano Classification.

- Rate of CR defined as the proportion of patients who achieves a best response of CR, assessed by IRC per the Lugano Classification.

- Time to Response (TTR) defined as the time from the date of the first dose of BGB-A317 to the time the response criteria is first met, assessed by IRC per the Lugano Classification.

- To evaluate the safety and tolerability of BGB-A317, as defined by:

- The incidence and severity of adverse events according to NCI-CTCAE v4.03
- Changes in vital signs, physical findings, and clinical laboratory results

4.3 CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

5 SAMPLE SIZE CONSIDERRATIONS

The sample size calculation is based on the power of the comparison to the historical control rate, and assumed an ORR of 55% in the study as compared to 35% in the historical control. Using a binomial exact test, the power is 0.912 with 68 patients in the modified Safety Analysis Set to demonstrate statistical significance at a one-sided alpha of 0.025. The 95% exact CI would be (0.425, 0.671), when the observed ORR is 0.55.

6 ANALYSIS POPULATIONS

The Safety Population (SAF) includes all patients who received any dose of BGB-A317. This will be the population for the safety analyses.

The modified Safety Population (mSAF) includes all patients in the Safety Population who had centrally confirmed relapsed or refractory cHL. This will be the primary population for the efficacy analyses.

The Per-Protocol Population (PP) includes patients who received any dose BGB-A317 and had no major protocol deviations. Criteria for exclusion from the PP will be determined and documented before the database lock for the primary analysis. Analyses of the PP for the primary endpoint might be included in the appendices if the size of the PP is significantly different from the size of that in the modified Safety population.

CCI [redacted]

[redacted]

7 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, 25 percentile (Q1), 75 percentile (Q3), minimum (Min), maximum (Max) and n. Categorical variables will be summarized as number (percentage) of patients.

7.1 DATA ANALYSIS GENERAL CONSIDERATIONS

7.1.1 Definitions and Computations

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

Study day: Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). 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; derivation of study Day and any corresponding durations when there is partial or missing date will be based on the imputations specified in Appendix 1.

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

Retests and Unscheduled Visits: Unscheduled measurements will not be included in by-visit table summaries and graphs, but will contribute to best/ worst case value where required (e.g. shift table). Listings will include scheduled, unscheduled and retest data.

All calculations and analyses will be conducted using SAS version 9.3 or higher.

7.1.2 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
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date rather than the associated visit date.
- 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.

7.1.3 Adjustments for Covariates

Not applicable.

7.1.4 Multiple Comparisons/Multiplicity

Not applicable.

7.1.5 Handling of Missing Data

Missing data will not be imputed unless 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, prior/concomitant medications/therapies/procedures and further anticancer therapy are provided in Appendix 1.

By-visit endpoints will be analyzed using non-missing observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed.

7.2 PATIENT CHARACTERISTICS

7.2.1 Patient Disposition

The number (percentage) of patients screened (those who signed the informed consent form), treated, discontinued from study drugs and discontinued from the study will be summarized. The primary reason for end of treatment (study drug discontinuation) and end of study will be summarized according to the categories in the eCRF.

CCI [redacted]

7.2.2 Protocol Deviations

Major protocol deviation criteria will be established and patients with major protocol deviations will be identified and documented before the database lock. Major protocol deviations will be summarized for all patients in the safety population. They will also be listed by each category.

7.2.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in both safety population and modified safety population.

Demographic characteristics include age in years (quantitative and qualitative variable: <65, ≥65-<75 and ≥75), gender (male, female), BMI (in kg/m^2), body weight (in kg), height (in cm), ECOG.

7.2.4 Disease History

The number (percentage) of patients reporting a history of disease and characteristic, as recorded in CRF, will be summarized in the modified safety population. Disease characteristics include cHL

subtype, time from initial diagnosis time to study entry, time from most recent progression relapse, International Prognostic Score (IPS) at diagnosis (for derivation of IPS, refer to Appendix 2), disease stage, Bulky disease, stage modifier and B symptoms, etc.

7.2.5 Medical History

Medical History will be coded using MedDRA codes of the version currently in effect at Beigene at the time of database 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 safety population. A listing of medical history will be provided.

7.2.6 Prior Systematic and Radiation Therapies

The information of prior systematic therapies, prior anti-cancer radiotherapy will be summarized in the modified safety population.

7.2.7 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD) drug codes of the version currently in effect at Beigene at the time of database lock, 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 in the safety population. Prior medications are defined as medications that stopped before the first dose date. 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.

7.3 EFFICACY ANALYSIS

7.3.1 Primary Efficacy Analyses

The overall assessment result by IRC per the Lugano Classification (Cheson et al, 2014) will be used in the primary efficacy analysis.

In relapsed or refractory cHL, ORR with single agent treatment as historical control is assumed to be approximately 35% based on historical trials. The ORR of BGB-A317 in this study is assumed as 55%, which is deemed a clinically meaningful improvement. Hence, the null and alternative hypotheses are set as follows:

H0: ORR = 35%
Ha: ORR > 35%

A binomial exact test will be performed for hypothesis testing in the modified Safety Population. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that the single agent BGB-A317

statistically significantly increases ORR compared with historical controls. Therefore, the superiority of single agent BGB-A317 will be demonstrated.

A two-sided Clopper-Pearson 95% CI of ORR will be constructed to assess the precision of the rate estimate.

Best Overall Response (BOR) is defined as the best response recorded from the first dose of BGB-A317 until data cut or start of new anti-neoplastic treatment. Patients with no post-baseline response assessment (due to any reason) will be considered non-responders for BOR. The proportion and its corresponding Clopper-Pearson 95% CI for each of the response categories will be presented in the relevant analysis population.

A swimmer lane plot of time on treatment (ie, duration of exposure), with indicators for the start and end of each response episode classified by CR or PR, will also be provided. The patients will be ordered by the duration of exposure. Patients with the longest duration will be presented at the top of the plot.

Supportive Analysis for ORR

ORR will be summarized in the modified safety population using the investigator assessment per the Lugano classification, as supportive analysis. The same methods used in the primary analysis (ORR by IRC) will be employed in this analysis.

7.3.2 Secondary Efficacy Analysis

Progression Free Survival (PFS)

PFS is defined as the time from the date of first study dose to disease progression or death whichever occurs first, assessed by IRC per the Lugano Classification.

Kaplan-Meier methodology will be used to estimate median or other quartiles of PFS along with its 95% confidence interval (constructed using Brookmeyer and Crowley method). Kaplan-Meier curves will be constructed to provide a visual description of the PFS distribution. Event free rate at selected timepoints will be estimated with 95% confidence interval using Greenwood formula.

The PFS censoring rules will generally follow US FDA's "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)".

Table 1 Censoring rules for PFS analysis

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline and/or post-baseline disease assessments	Date of the first dose	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first disease assessment showing with documented disease progression	Progressed
3	Alive without documented disease progression at the time of data cut-off or withdrawal from study (including lost-to-follow-up without disease progression)	Date of last disease assessment	Censored
4	New anticancer treatment started	Date of last disease assessment prior to new anticancer treatment start	Censored
5	Death before first disease assessment	Date of death	Progressed
6	Death or progression after more than one missed scheduled disease assessment	Date of last disease assessment without documented disease progression before missed tumor assessments	Censored

Analyses of PFS by investigator per Lugano Classification will also be calculated using same censoring rules and analysis methods for PFS by IRC.

Duration of Response (DOR)

Duration of Response (DOR) by IRC per Lugano Classification will be analyzed similarly as PFS. Among mSAF, only patients who have achieved an objective response of PR or above will be included in the analysis of DOR. For patients who are alive without progression following the qualifying response, duration of response will be censored following the same censoring rules as PFS. DOR by investigator per Lugano Classification will also be calculated.

Time to Response (TTR)

Time to Response (TTR) by IRC will be analyzed using sample statistics such as mean, median and standard deviation among mSAF who have achieved an objective response. TTR by investigator will also be summarized similarly.

Complete Response (CR) rate

Complete Response (CR) rate by IRC will be summarized in the Modified Safety Population as part of BOR summary results. Its Clopper-Pearson 95% CI will be calculated. CR rate by investigator will be summarized similarly.

7.3.3 CCI

CCI [redacted]

7.3.4 Subgroup Analyses

Primary and selected secondary endpoints will be summarized descriptively with respect to following demographic/baseline characteristics and prognostic subgroups: gender, age group (<65 vs ≥65), ECOG (0 vs 1), prior line of therapy for cHL (<3 vs ≥3), bulky disease (yes vs no), prior transplant (yes vs no), if deemed necessary and when there is sufficient number of patients in the subgroup, otherwise relevant subgroups may be combined.

Within each selected subgroup the treatment effect will be analyzed similarly using methods describe above among mSAF population. For each subgroup and for the overall population, the estimation of treatment effect and corresponding 95% CI will be displayed using forest plot.

A summary of the analyses needed for all the efficacy endpoints are briefly described in Table 2.

Table 2 Description of analyses to be provided for efficacy endpoints

Endpoint	Population	Primary Analysis	Statistical method	Supportive Analysis
Primary Endpoint				
ORR	mSAF	Compare with historical control rate; estimation and 95% CI of ORR, by IRC per Lugano classification	Binomial exact test; Clopper-Pearson 95% CI	Analysis of ORR assessed by Investigator per Lugano classification; Subgroup analysis
Secondary Endpoint				
PFS	mSAF	Estimation of median PFS and its 95% CI, using data assessed by IRC per Lugano classification	Kaplan-Meier method	Analysis of PFS by Investigator per Lugano
DOR	Patients in	Estimation of median DOR and	Kaplan-Meier	Analysis of DOR by Investigator

	mSAF w/ objective response	its 95% CI, by IRC per Lugano classification	method	per Lugano
TTR	Patients in mSAF w/ objective response	TTR assessed by IRC per Lugano classification	Descriptive statistics	Analysis of TTR by Investigator per Lugano
CR rate	mSAF	CR assessed by IRC per Lugano classification	Clopper-Pearson 95% CI	CR assessed by Investigator per Lugano classification
CCI				
C				
CI				

7.4 SAFETY ANALYSES

All safety analyses will be performed based on SAF. The incidence of treatment-emergent adverse events and SAEs will be summarized. Laboratory test results, vital signs and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables. Abnormal values will be flagged.

7.4.1 Extent of Exposure

The BGB-A317 dose information of each patient will be assessed by the following variables:

- Number of treatment cycles started equals to the count of cycles with BGB-A317
- Duration of exposure (weeks) is defined as:

(date of last dose of BGB-A317 + 21 days – date of first dose of BGB-A317)/7

- Cumulative dose (mg): the sum of all actual doses of BGB-A317, given from first to last administration
- Actual dose intensity (ADI) in mg/week is defined as:

Cumulative dose (mg) / Duration of exposure (week)

- Relative dose intensity (RDI) in % is defined as:

$$100 \times \frac{\text{ADI (mg/week)}}{\text{Planned Dose Intensity (mg/week)}}$$

Where Planned dose intensity equals to 200/3 mg/week.

Number of cycles started by patient as a quantitative variable and by category (ie, number (%) of patient receiving at least 1 cycle, at least 2 cycles etc), duration of exposure, cumulative dose, ADI and RDI will be summarized by descriptive statistics.

The following analyses will be performed to describe BGB-A317 dose modifications:
The number (percentage) of patients requiring dose interruption and dose delay due to AEs will be summarized. The cycle in which the first dose interruption/delay occurred will be summarized using descriptive statistics. Frequency of dose interruptions/delay will be summarized by categories.

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

7.4.2 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 (LLT) 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 or a worsening in severity from baseline (pre-treatment) on or after the first dose of study drug up to 90 days following study drug discontinuation, regardless of whether or not the patient starts a new anti-cancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

An overview of patients with at least one TEAE will be presented with the incidence of:

- patients with any TEAE
- patients with any TEAE with grade 3 or higher
- patients with any serious TEAEs
- patients with any TEAE leading to death
- patient with any TEAE leading to treatment discontinuation
- patients with any TEAE leading to dose modification, including dose interruption and dose delay
- patients with any treatment-related TEAE

- patients with any treatment-related TEAE with grade 3 or higher
- patients with any treatment-related serious TEAEs
- patients with any treatment-related TEAE leading to death
- patient with any treatment-related TEAE leading to treatment discontinuation
- patients with any treatment-related TEAE leading to dose modification, including dose interruption and dose delay
- patients with any irTEAE

where treatment-related AEs include those events considered by the Investigator to be definitely, possibly, or probably related to study treatment or with missing assessment of the causal relationship. For patients with multiple occurrences of the same event will be counted only once, and the maximum grade per CTCAE v4.03 will be used.

The incidence of following TEAEs will be reported by SOC and PT, sorted by decreasing frequency of system organ class and preferred term:

- TEAE (any grade)
- TEAE displayed by maximum severity
- TEAE leading to treatment discontinuation displayed by maximum severity
- TEAE leading to treatment modification (interruption or delay) displayed by maximum severity
- TEAE leading to death
- Immune-related TEAE displayed by maximum severity
- TEAE with grade 3 or higher displayed by maximum severity
- Treatment-related TEAE displayed by maximum severity
- Serious TEAE displayed by maximum severity
- Serious related TEAE displayed by maximum severity

The incidence of following TEAEs will be reported by PT, in descending order:

- TEAE (any grade)
- TEAE leading to treatment discontinuation displayed by maximum severity
- TEAE leading to treatment modification (interruption or delay) displayed by maximum severity
- TEAE leading to death

- TEAE with grade 3 or higher displayed

Patient data listings of all AEs leading to death, treatment-related AE, grade 3 or above AEs, SAEs, AEs leading to discontinuation from study drug will be provided.

CCI [redacted]

7.4.3 Laboratory Values

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

Laboratory parameters that are graded in NCI CTCAE (v.4.03) will be summarized by shifts from baseline CTCAE grades to maximum 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.

Patient data listings of selected laboratory parameters will be provided

7.4.4 Vital Signs

Descriptive statistics for vital signs parameters (i.e., resting diastolic and systolic BP, resting pulse rate, respiratory rate, temperature) and changes from baseline will be summarized by visit.

7.4.5 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. Postbaseline observations and Change from baseline of QTc will be summarized.

7.4.6 ECOG

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized. ECOG scores will be summarized by visit.

7.5 CCI [redacted]

7.6 CCI [redacted]

8 INTERIM ANALYSES

No interim analysis is planned. Safety monitoring will be conducted continuously through end of treatment visit.

9 CHANGES IN THE PLANNED ANALYSIS

Not applicable so far.

10 REFERENCES

CCI [redacted]

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11 APPENDIX

11.1 APPENDIX 1 MISSING DATA IMPUTATION

Handling 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:

1. 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 start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

   If end date of an adverse event 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 end date is completely missing, do not impute
2. 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

- For prior anticancer therapy, the imputed end date should be the first dose date – 14 at the latest after imputation.

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

3. If the first diagnosis of cHL 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 most recent progression relapse date 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 first diagnosis date and most recent relapse date is completely missing, do not impute.

Handling of missing grades of adverse events

If the grade is missing for one of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences with the same preferred term will be used. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

11.2 APPENDIX 2 INTERNATIONAL PROGNOSTIC SCORE

- Male sex (1 point)
- Age ≥ 45 years (1 point)
- Stage IV (1 point)
- Hemoglobin < 10.5 g/dL (1 point)
- WBC ≥ 15 x 10^9/L (1 point)
- Lymphocyte count < 0.6 x 10^9/L or < 8% of differential (1 point)
- Albumin < 4 g/dL (1 point)