STATISTICAL ANALYSIS PLAN

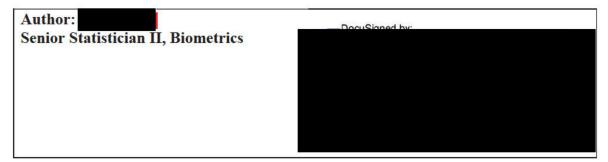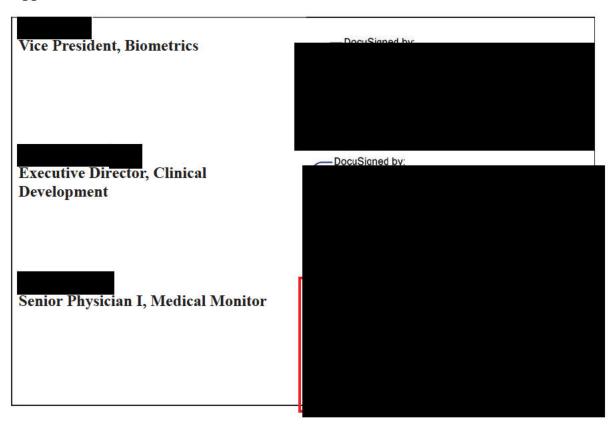|	
Study Protocol Number:	BGB-290-201
Study Protocol Title:	An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China
Date:	OCT 13, 2020
Version:	1.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the plasma concentration-time curve
AUC_{0-12h}	area under the plasma concentration-time curve from zero to 12 hours post-dose
BC	breast cancer
BID	twice daily
BGB-290	study drug code
BOR	best overall response
BP	blood pressure
BRCA	breast cancer susceptibility gene
CBR	clinical benefit rate
CD8	cluster of differentiation 8
CI	confidence interval
C_{max}	maximum observed plasma concentration
C_{min}	minimum observed plasma concentration
CR	complete response
DCR	disease control rate
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
FDA	Food and Drug Administration
HER2(-)	human epidermal growth factor receptor 2-negative
HR(+)	hormone receptor-positive
ICF	informed consent form
IRC	independent radiology review
MDS/AML	myelodysplastic syndrome/acute myeloid leukemia
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events

NE	not evaluable
ORR	objective response rate
OS	overall survival
PA	protocol amendment
PARP	poly(ADP-ribose) polymerase
PD-L1	programmed death-ligand 1
PFS	Progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PT	preferred term
QTc	QT interval corrected for heart rate
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	system organ class
TEAE	Treatment-emergent adverse event
TNBC	triple negative breast cancer
TTR	time to response
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-290-201: An Open Label, Multi-Center Phase 2 Study to Evaluate Efficacy and Safety of BGB-290 in the Treatment of Metastatic HER2-Negative Breast Cancer Patients with *BRCA* mutation in China. The focus of this SAP is for the planned analysis specified in the study protocol.

The analysis details for Pharmacokinetic (PK), Pharmacodynamics, Pharmacogenomics and Biomarker analyses are not described within this SAP.

Reference materials for this statistical plan include the protocol BGB-290-201 (30OCT2018) and Case Report Forms (1JUN2020). If the protocol or case report forms are amended or updated, then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an *a priori* plan. This is an open label study and the SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate to have analysis programs ready at the time of study end.

2 STUDY OVERVIEW

This is a Phase 2, open-label, multi-center study of BGB-290 administered PO BID in adult Chinese patients with advanced HER2(-) breast cancer harboring germline *BRCA* mutation, which have progressed despite standard therapy, or for which no standard therapy exists. In this study, the efficacy, safety, tolerability, and PK profile of BGB-290 will be further evaluated. All eligible patients will be enrolled into one of the below cohorts:

1. Approximately 55 evaluable previously treated patients with locally advanced or metastatic TNBC with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation

2. Approximately 20 previously treated patients with locally advanced or metastatic HR(+)/HER2(-) breast cancer with confirmed either deleterious or suspected deleterious germline *BRCA1/2* mutation

Patients will be screened for eligibility up to 28 days prior to the first dose of BGB-290 and will take BGB-290 at 60 mg BID continuously for all cycles (28-day cycles) starting on Day 1 of Cycle 1. Patients will be instructed to swallow the capsules whole, in rapid succession, with water. BGB-290 can be administered with or without food.

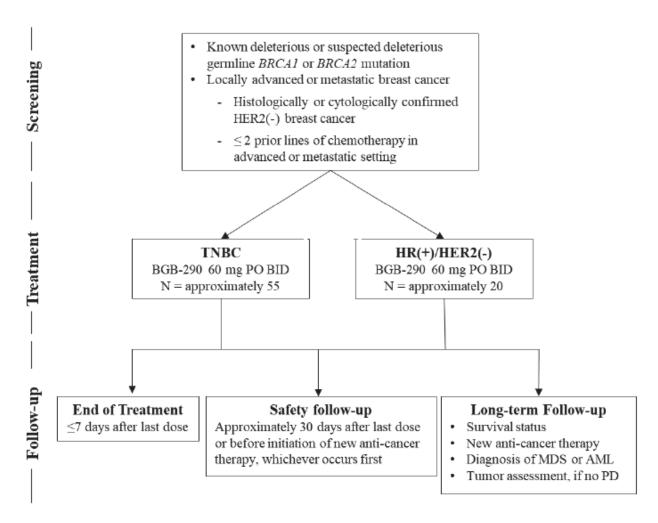Tumor response will be assessed by independent radiology review (IRC) and investigators based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1).

Patients will be monitored for safety, tolerability, and efficacy throughout the study. Tumor assessments will be performed every 8 weeks $\pm$ 7 days in the first year, and then every 12 weeks $\pm$ 7 days thereafter, or as clinically indicated.

Patients will continue treatment until occurrence of disease progression as assessed by the investigator, unacceptable toxicities, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Figure 1. Study Schema

Abbreviations: BC, breast cancer; BID, twice daily; HER2(-), human epidermal growth factor receptor 2 negative; HR(+), hormone receptor-positive; PD, progression disease; PO, oral; TNBC, triple negative breast cancer.

Note: Key assessments during treatment phase: tumor assessments every 8 weeks ± 7 days in the first year and every 12 weeks ± 7 days in the second year and above. Hematology assessments every 2 weeks in Cycles 1 and 2, then every 4 weeks in subsequent cycles. Adverse events at each visit. Chemistry assessments every 4 weeks throughout the study. BGB-290 is to be administered continuously.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the efficacy of BGB-290 in patients with advanced triple negative breast cancer or HR(+)/HER2(-) breast cancer harboring germline *BRCA1/2* mutation, as measured by

Overall Response Rate (ORR) according to RECIST v1.1 by IRC.

3.2   SECONDARY OBJECTIVES

- To further evaluate the efficacy of BGB-290 in patients with TNBC or HR(+)/HER2(-) breast cancer harboring germline *BRCA1/2* mutation, as measured by ORR according to RECIST v1.1 by investigator assessment; Progression-free survival (PFS) and duration of response (DOR) by IRC and investigator assessment; Disease control rate (DCR), best overall response (BOR) and clinical benefit rate (CBR) assessment by IRC and investigator assessment; Overall survival (OS).

- To evaluate the safety and tolerability of BGB-290.

3.3   EXPLORATORY OBJECTIVES

4   STUDY ENDPOINTS

4.1   PRIMARY ENDPOINTS

- ORR is defined as the proportion of patients who achieved a best overall response of complete response (CR) or partial response (PR), assessed by IRC per RECIST v1.1. Secondary Endpoints

- ORR is defined as the proportion of patients who achieved a best overall response of CR or PR, assessed by investigator per RECIST v1.1. Both confirmed and unconfirmed ORR will be summarized.

- PFS is defined as the time from first dose of BGB-290 to the first documented disease progression assessed by IRC and investigator per RECIST v1.1 or death due to any cause.

- DOR is defined as the time from first determination of a confirmed best overall response until the first documentation of progression or death, whichever comes first, assessed by IRC and investigator per RECIST v1.1.

- BOR is defined as the best overall response recorded from the start of the treatment until disease progression/recurrence, assessed by IRC and investigator per RECIST v1.1. Both confirmed and unconfirmed BOR will be summarized.

- DCR is defined as the proportion of patients who achieved a confirmed BOR of CR, PR, or stable disease (SD) assessed by IRC and investigator per RECIST v1.1.

- CBR is defined as proportion of patients with confirmed CR or confirmed PR or a durable SD (SD lasting $\geq$ 24 weeks) assessed by IRC and investigator per RECIST v1.1.

- OS is defined as time from the first dose of BGB-290 to the date of death due to any cause.

- Incidence, timing, and severity of treatment-emergent adverse events graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.03 (Common Toxicity Criteria Version 4.03) or higher; changes in vital signs, physical findings, and clinical laboratory results.

4.2   EXPLORATORY ENDPOINTS

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5   SAMPLE SIZE CONSIDERATIONS

A total of approximately 75 patients will be enrolled into one of the below cohorts.

- Approximately 55 evaluable patients will be enrolled into the TNBC cohort. In TNBC cohort, it is assumed that ORR is 46% in patients with BGB-290. There is an 90% power of demonstrating a statistical difference versus a historical response rate of 25% using a binomial exact test at an alpha of 0.025 in 55 evaluable patients. The 2-sided exact 95% CI is (32.0%, 59.5%) when the observed ORR is 46%. Additional patients may be enrolled to meet the required number of evaluable patients.

- Approximately 20 patients will be enrolled into the HR(+)/HER2(-) breast cancer cohort. This is an exploratory cohort.

6   STATISTICAL METHODS

All analyses in this section will be presented by cohort side by side, unless otherwise specified.

6.1   ANALYSIS SETS

Safety Analysis Set: includes all patients who receive at least one dose of BGB-290.

Efficacy Evaluable Analysis Set: includes all patients in the safety population who have measurable disease at baseline per RECIST v1.1 by IRC and have at least one evaluable post baseline tumor assessment by IRC unless discontinued treatment due to clinical progression or death prior to tumor assessment.

PK Analysis Set: includes all patients in the safety population who have at least 1 quantifiable PK sample for BGB-290.

6.2   DATA ANALYSIS GENERAL CONSIDERATIONS.

6.2.1   Definitions and Computations

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. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 10.1.

Treatment duration: The treatment duration will be calculated as (date of the last non-zero dose of study drug – date of first dose of study drug + 1).

Baseline: the non-missing value most recently collected before the first dose.

All calculations and analyses will be conducted using SAS version 9.4 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 decimal place.

- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 decimal place.

- 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 the radiograph was obtained rather than the associated visit date.

- Missing efficacy or safety data will not be imputed unless otherwise specified.

- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.

- 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, Q1, Q3 and range (minimum and maximum).

6.2.3   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. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 10.1.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

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.

At the time of efficacy analysis, if death or disease progression is not observed from a patient, corresponding censoring rules for OS, DOR and PFS will be followed.

6.2.4   Adjustment for Covariates

No adjustments for covariates are planned for primary, secondary and exploratory analyses in the study.

6.2.5   Multiplicity Adjustment

No multiplicity adjustments will be made in this study. Two-sided 95% confidence interval will be used to describe the precision of the rate estimate whenever appropriate.

6.2.6   Data Integrity

Before pre-specified final statistical analysis begins, the integrity of the data will be reviewed to assure fit-for-purpose. The data set for analysis will be an accurate and complete representation of the subjects' relevant outcomes from the clinical database. All data will be complete and reviewed up to a pre-specified cutoff date. Consistency checks and appropriate source data verification will be complete.

6.3   SUBJECT CHARACTERISTICS

6.3.1   Subject Disposition

The number (percentage) of patients treated, discontinued from study treatment, entered survival follow-up, discontinued from study (including those who discontinued study treatment and did not enter survival follow-up, and those discontinued from the survival follow-up) and duration of follow-up will be summarized. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF. The survival end of study status (alive, death,

withdrew consent or lost to follow-up) at the data cutoff date will be listed using the data from the eCRF.

6.3.2   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 analysis set. They will also be listed by each category.

6.3.3   Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the safety analysis set, using descriptive statistics.

Continuous demographic and baseline variables include age, BMI, body weight, and height; categorical variables include age group (< 50 years, 50 – 65 years, > 65 years), race, ECOG performance status at study entry. In addition, disease characteristics include types of cancer, tumor staging, tumor diagnosis, metastasis status, germline BRCA mutation type and time from initial diagnosis.

6.3.4   Prior Anti-Cancer Drug Therapies, Surgeries and Radiotherapies

The number of line, type, best response and duration of prior systemic treatment will be summarized in safety analysis set. The therapies with the same line number are counted as one prior therapy.

Previous anticancer medication will be summarized in the World Health Organization Drug Dictionary (WHO DD) preferred term..

6.3.5   Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO DD 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 by phase in the safety analysis set. 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 or initiation of a new anticancer therapy, whichever occurs first. A listing of prior and concomitant medications will be provided.

6.3.6   Medical History

Medical/disease history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher). The number (percentage) of patients reporting a history of any

medical condition, as recorded on the eCRF, will be summarized by system organ class and preferred term in the safety analysis set. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

6.4.1 Primary Efficacy Endpoints

ORR by IRC is defined as the proportion of patients who achieves a best overall response of complete response (CR) or partial response (PR), assessed by IRC per RECIST v1.1.

TNBC cohort

Hypothesis testing of ORR by IRC will be performed in the Efficacy Analysis Set.

ORR of BGB-290 per IRC is assumed as 46% in patients with TNBC. The historical rate in a similar population is estimated as 25%. The null and alternative hypotheses are set as follows:

$$H_0: \text{ORR}= 25\%$$

$$H_a: \text{ORR} > 25\%$$

A binomial exact test will be performed for hypothesis testing in the Efficacy Analysis Set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that BGB-290 monotherapy statistically significantly increases ORR compared with historical control. A two-sided binomial exact 95% CI of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated at 6th month after the last patient received the first dose of study drug. In addition, the duration of treatment will be presented in swimmer plot. The tumor size change from baseline will be presented as in a waterfall plot in the efficacy evaluable analysis set.

HR(+)/HER2(-) breast cancer cohort

ORR by IRC and its two-sided binomial exact 95% CI will be calculated similarly as described above in the TNBC cohort. However, no statistical comparison to a specified historical rate is planned.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will be analyzed in the TNBC and HR(+)/HER2(-) cohorts. Kaplan-Meier method will be used to estimate the DOR by IRC and DOR by INV, and corresponding quartiles (including the median) in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method.

Duration of response analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule which will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

Table 2 shows the primary censoring rules for the derivation of PFS using RECIST v1.1 criteria based upon tumor assessment.

Table 2. Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Reference start date	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 cutoff or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cutoff or withdrawal from study	Censored
4	Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
5	New anticancer treatment started	Date of last radiological assessment of measured lesions prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Progressed
7	Death between adequate assessment visits*	Date of death	Progressed
8	Death or progression after two or more consecutive missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

**More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 2 scheduled visits + one time window.

Other time-to-event analysis endpoints (PFS by IRC, PFS by INV and OS) will be analyzed in the safety analysis set using the Kaplan-Meier method. The Kaplan-Meier estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time point (eg, 3 or 6 months), will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula. The OS time point estimates will be calculated similarly. For OS analysis, patients with no death date in the database will be censored at the last date the patient was known to be alive before/on cutoff date.

BOR is defined as the best response recorded from the start of BGB-290 until data cutoff or start of new antineoplastic treatment. BOR and their 95% CIs will be summarized in the efficacy evaluable analysis set. Sensitivity analysis of BOR will be carried out in the safety analysis set. The proportion of each response category (CR, PR, SD, PD and NE) will be presented for both efficacy evaluable analysis set and safety analysis set.

DCR and CBR and their 95% CIs will be summarized for the efficacy evaluable analysis set and safety analysis set.

Time to response (TTR) is defined as the time from first dose date to the date of earliest confirmed response (CR or PR) assessed using RECIST V1.1. TTR will be summarized descriptively.

All the efficacy endpoints will be summarized by cohort. Assessments by IRC and investigator will be summarized separately. The concordance rate between IRC and INV assessed BOR and ORR will be evaluated.

6.4.3 Subgroup Analyses

Subgroup analyses of ORR will be conducted separately for both TNBC and HR(+)/HER2(-) cohorts. Table and forest plot of subgroup analysis in ORR will be provided based on the following subgroups:

- Age group (< 50 years vs. $50 - 65$ years vs. > 65 years)
- Baseline ECOG performance status (0 vs. 1)
- BRCA mutation type (BRCA1 vs. BRCA2)
- Number of prior chemotherapy lines (0 vs. 1 vs. ≥ 2)
- Prior Platinum-based Systemic Chemotherapy (Yes vs. No)
- Number of metastatic sites (1 vs 2 vs ≥ 3)
- Visceral metastasis (Yes vs No)
- Brain metastasis (Yes vs No)

For the HR(+)/HER2(-) cohort, an additional subgroup analysis will be conducted.

- ER/PgR status (ER or PgR $\geq 10\%$ vs ER and PgR $<10\%$ vs ER or PgR Unknown)

These planned subgroup analyses may not be explored if enough samples cannot be achieved for certain subgroups. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

6.4.4 Exploratory Efficacy Endpoints

6.5 SAFETY ANALYSES

All safety analyses will be performed by cohort based on the safety analysis set. The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized. Laboratory test results, vital signs, ECG 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.

6.5.1 Extent of Exposure

The number (and percentage) of patients requiring dose reductions, dose interruption, and treatment discontinuation will be summarized.

The duration of treatment (months) will be summarized with descriptive statistics. It will be calculated as (Date of last non-zero dose – Date of first dose + 1) / 30.4375.

Number of patients with dose reductions and treatment discontinuation and their reasons, as well as number of patients with any dose modification will be summarized by counts and percentages according to study medication data. In addition, frequency of dose reductions and dose interruption will be summarized by categories (0, 1, ≥2).

Average dose intensity per patient (in mg/day) and relative dose intensity (total dose received / total dose planned) per patient will be summarized. Average dose intensity is calculated as the total dose (mg) taken by a patient divided by overall duration of exposure (= Date of last non-zero dose – Date of first dose + 1) for individual patient. Relative dose intensity is calculated as the total dose (mg) taken by a patient divided by the total dose planned for the patient by study design, e.g. 60 mg BID.

Patient data listings will be provided for all dosing records.

6.5.2 Adverse Events

AEs will be graded by the investigators using CTCAE version 4.03 or above. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA, version 22.0 or higher, 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 TEAE is defined as an AE that had an onset date or was worsening in severity from baseline (pretreatment)on or after the first dose of study drug up to 30 days following study drug discontinuation. All AEs will be included in the listings and only TEAEs will be included in the summary tables. SAEs, deaths, TEAEs with Grade 3 or higher, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

The attribution of TEAEs to the study drug are categorized by investigators according to the 5-item scales, including not related, unlikely related, possibly, probably related and definitely related. The primary definition of the treatment-related TEAEs uses the 3 to 2 mapping, including those events considered by the investigator to be possibly or probably or definitely- related to study drug or with missing assessment of the causal relationship. The 4 to 1 mapping will also be explored in addition to the primary definition in the compliance with the agency requirements. In the 4 to 1 mapping, the TEAEs assessed by the investigator to be unlikely related to the study drug will also be considered treatment related.

An overview table, including the incidence and the number of patients with TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with Grade 3 or higher, treatment-related treatment-emergent SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. The above analyses will repeat for the treatment-related TEAEs defined in either the 3 to 2 or the 4 to 1 mapping.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade according to CTCAE version 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, TEAEs with Grade 3 or higher, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized by SOC and PT. The treatment-related TEAEs will also be summarized by SOC and PT for the above categories. TEAEs and treatment related TEAE with grade 3 or higher will also be summarized by PT in descending order.

Patient data listings of all AEs, SAEs, treatment-related AEs, grade 3 or higher AEs, AEs that led to death and AEs that led to treatment discontinuation will be provided.

6.5.3   Laboratory Values

Laboratory safety tests (hematology, which is reviewed prior to BGB-290 administration, serum chemistry assessed on Day 1 of every cycle, and pregnancy test assessed at screening and EOT) will be assessed in the study.

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Table 3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit using descriptive statistics. Qualitative parameters listed in Table 3 will be summarized using frequencies (number and percentage of patients), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of patients with non-missing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to NCI CTCAE version 4.03 grades and shifts from baseline CTCAE grades to maximum and the last postbaseline grades will be assessed. Laboratory parameters will be summarized by worst postbaseline CTCAE grade as well. For the lab tests with both high and low abnormality, separate records of worst CTCAE grade (for high and low) will be generated.

Table 1. Serum Chemistry and Hematology Laboratory Tests

Serum Chemistry	Hematology
Alkaline phosphatase (ALP)	Hemoglobin
Alanine aminotransferase (ALT)	Platelet counts
Aspartate aminotransferase (AST)	White blood cell (WBC) count

Albumin	Neutrophil (Absolute)
Total bilirubin	Lymphocyte (Absolute)
Creatinine	
Phosphate	
Glucose	
Potassium	
Sodium	
Urea	
Total protein	
Blood urea nitrogen	
Chloride	
Lactate dehydrogenase	

6.5.4   Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], pulse rate, temperature, and respiratory rate) and changes from baseline for all pre-dose assessments will be presented by visit. Vital signs will be listed by patients, visits and timepoints.

6.5.5   Electrocardiograms

ECG will be performed at baseline and the end of treatment visit. Patient listing of ECG will be provided for all ECG recordings with the indicator whether the abnormality is clinical significance.

6.5.6   ECOG Performance Status

ECOG scores will be summarized by visit.

6.6   PHARMACOKINETIC ANALYSES

BGB-290 concentrations after single-dose and at steady-state will be summarized by the sampling timepoint. Descriptive statistics will include means, medians, and standard deviations, as appropriate.

6.7   AD HOC ANALYSES

Protocol version 1.0 was released on 30 October 2018, which was in the middle of study conduct. The new version of the protocol provided a more proactive dose modification algorithm and closer hematology monitoring in early stage of drug administration to improve hematological safety management.

The analysis of hematological safety data comparison of BGB-290 between pre- and post- protocol amendment (PA) is proposed. Post-PA subgroup is defined as patients signed the first ICF under protocol version 1.0 and Pre-PA subgroup includes patients who signed first ICF under at least one previous protocol version. The detailed description of the analysis is in Appendix 10.2.

6.8 COVID-19 IMPACT ANALYSIS

Impact of the COVID-19 on the study conduct will be summarized and listed.

The COVID-19 impact on the patient disposition, including treatment and study discontinuation, will be summarized. The delay or missing of study visit, lab assessments due to COVID-19 will also be summarized. The missed and delayed tumor assessment as well as tumor assessment done at auxiliary sites will be summarized. For the safety analysis, the modification and discontinuation of study drug as well as COVID-19-related AE will be summarized if applicable. In addition, the major protocol deviation due to COVID-19 will be listed.

7 INTERIM ANALYSIS

No formal interim analysis is planned.

8 CHANGES IN THE PLANNED ANALYSIS

No changes are identified.

9 REFERENCES

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10 APPENDIX

10.1 IMPUTATION OF PARTIAL DATES FOR AEs/MEDICATIONS/THERAPIES/PROCEDURES

IMPUTATION FOR AEs WITH MISSING OR PARTIAL DATES

If AE start/end date are missing or partial missing, the following imputation rules apply.
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 the imputed end date > death date, then set to death date

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

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 start date is completely missing, do not impute.

If the imputed start date > death date, then set to death date. If the imputed start date > the end date (or the imputed end date), set the imputed start date = end date (or the imputed end date).

IMPUTATION FOR MEDICATIONS/THERAPIES/PROCEDURES WITH MISSING OR PARTIAL DATES

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 medication/therapy/procedure:

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 the imputed start date > death date, then set to death date

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 imputed end date > death date, then set to death date

- For prior anticancer therapy (radiotherapy, systemic therapy), the imputed end date should be the first dose date – 15 at the latest after imputation.

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.

For detailed imputation rule for new anti-cancer therapy and death date, etc., please refer to a separate document "Standard Definitions and Derivation Rules of Key Variables_V1".

10.2 PRE- AND POST- PROTOCOL AMENDMENT (PA) HEMATOLOGICAL ANALYSES

The following safety data is considered for this analysis of comparison between pre- and post-PA:

C1. Summary of Hematology Laboratory Values

The hematological laboratory values at baseline will be summarized descriptively. The incidence of abnormal hematology values at baseline and any postbaseline visits, and number of patients (%) with shifts in hematology results of ≥ 2 toxicity grades from baseline to worst postbaseline grade will be summarized. The hematological laboratory parameters (unit) of interest for these summaries are: Hemoglobin (g/L), Leukocytes (10^9/L), Lymphocytes (10^9/L), Neutrophils (10^9/L), Platelets (10^9/L).

C2. Summary of Hematological TEAEs

An overall summary of hematological TEAEs will summarize the number (%) of patients. Summaries of the following hematological TEAEs will be provided:

- All hematological TEAEs by preferred terms
- Hematological TEAEs grade 3 or higher by preferred terms
- Serious hematological TEAEs by preferred terms

Hematological TEAE preferred terms are Anemia, Leukopenia, White blood cell count decreased, Neutropenia, Neutrophil count decreased, Thrombocytopenia, Platelet count decreased, Lymphopenia, Lymphocyte count decreased, Haemoglobin decreased, Erythropenia, Red blood cell count decreased, Bone marrow failure, and Febrile neutropenia.

C3. Extent of Exposure and Dose Modification

The following measures of overall extent of study drug exposure in patients between pre- and post-PA will be summarized:

- Duration of treatment (months), defined as (earlier of date of last nonzero dose and data cutoff date – date of first dose + 1) / 30.4375

- Number (%) of patients in each treatment duration category

- Number (%) of patients with dose modification (interruption and reduction)

- Number (%) of patients with dose interruptions and reasons of dose interruptions

- Number (%) of patients with dose reductions and reasons of dose reductions

- Time to first dose reduction (weeks), defined as (earlier of date of first nonzero dose date – date of first dose + 1) / 30.4375 for patients with dose reduction

C4. Concomitant Medications for Anemia

Erythropoietin and Red Blood Cell Transfusion related concomitant medications coded by the WHO-DD drug codes are identified as concomitant medications to cure anemia and will be further classified to the grouping drug name for this analysis of comparison on patients between pre- and post-PA. The number (%) of patients reporting concomitant medications for anemia will be summarized by two grouping drug names and its corresponding WHO-DD preferred terms as following:

EPO (Erythropoietin)
- Erythropoietin Human
- Erythropoietin
- Epoetin Beta

Red Blood Cell Transfusion
- Red Blood cells, Concentrated
- Human Red Blood Cells
- Blood, Whole
- Red Blood Cells
- Erythrocyte
- Red Blood Cells, Leucocyte Depleted

10.3 PROGRAMMING RULE

For detailed programming rule, please refer to a separate document "Standard Definitions and Derivation Rules of Key Variables_V1".