16.1.9 DOCUMENTATION OF STATISTICAL METHODS

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-290-103
Study Protocol Title:	A Phase 1b Study to Assess the Safety, Tolerability, and Clinical Activity of BGB-290 in Combination with Temozolomide (TMZ) in Subjects with Locally Advanced or Metastatic Solid Tumors
Date:	January 27, 2021
Version:	2.0

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the plasma concentration-time curve (drug exposure)
AUC_{0-12}	area under the plasma concentration-time curve from 0 to 12 hours postdose
BGB-290	pamiparib
CI	confidence interval
CKD-EPI	Chronic Kidney Epidemiology Collaboration
CR	complete response
CSR	clinical study report
CT	computed tomography
CTC	circulating tumor cell
CTC-HRD-negative or CTC-HRD-	circulating tumor cells negative for homologous recombination deficiency per Epic Sciences assay
CTC-HRD-positive or CTC-HRD+	circulating tumor cells positive for homologous recombination deficiency per Epic Sciences assay
CYP	cytochrome P450
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End-of-Treatment (Visit)
FDG	fluorine-18 [F-18]fluorodeoxyglucose
HBV	hepatitis B virus
HCV	hepatitis C virus
HRD	homologous recombination deficiency
IC_{50}	half-maximal inhibition concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRC	Independent Review Committee
mCRPC	metastatic castration-resistant prostate cancer
MDRD STUDY EQ	Modification of Diet in Renal Disease study equation
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging

Abbreviation	Definition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease
PET	positron-emission tomography
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
QTcF	QT interval with Fridericia's correction
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SD	stable disease
TEAE	treatment-emergent adverse event
TMZ	Temozolomide
ULN	upper limit of normal
US or USA	United States or United States of America

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 the efficacy and safety endpoints for protocol BGB-290-103: A Phase 1b Study to Assess the Safety, Tolerability, and Clinical Activity of BGB-290 in combination with Temozolomide (TMZ) in Subjects with Locally Advanced or Metastatic Solid Tumors. The focus of this SAP is for the planned primary, secondary and exploratory efficacy and safety analyses.

The analysis details for Pharmacokinetic (PK), Pharmacodynamics, Pharmacogenomics, and Biomarker analyses may not be fully described within this SAP. Separate analysis plans may be provided if applicable.

2 FOR THESE ANALYSES AND WILL BE ATTACHED TO THE CLINICAL STUDY REPORT STUDY OVERVIEW

This is an open-label, multi-center Phase 1b study to evaluate the combined use of pamiparib (also known as BGB-290), a poly (ADP-ribose) polymerase, e.g., PARP, inhibitor, with a deoxyribonucleic acid (DNA)-alkylating agent, TMZ, in subjects with locally advanced and metastatic solid tumors. The study consists of two phases, a dose escalation phase and a dose expansion phase. The dose escalation phase of the study will evaluate the safety, tolerability, preliminary efficacy, and PK in addition to determining the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) for the combination. In the dose expansion phase of this study, the safety, preliminary efficacy and PK profile of the combination will be evaluated further. Preliminary biomarkers for efficacy will also be explored through both phases of the study.

Dose Escalation:
The dose escalation phase of the study consists of a modified 3+3 dose escalation scheme utilizing a fixed dose of BGB-290 in combination with escalating doses of TMZ. The following two arms were planned to undergo dose escalation independently:

- Arm A: TMZ will be administered once a day during Days 1 to 7 of each 28-day cycle (pulse dosing of TMZ)
- Arm B: TMZ will be administered once a day continuously during each 28-day cycle (continuous dosing of TMZ)

Dose Expansion:
The dose expansion phase of the study will further evaluate the safety and anti-tumor activity of BGB-290 in combination with TMZ at the dose and schedule that will be chosen based on all data available including the dose escalation phase. This dose expansion phase will enroll patients in 6 different cohorts according to indication and/or homologous recombination deficiency (HRD) status as follows:

- Cohort 1: HRD positive (HRD+) ovarian cancer;
- Cohort 2: HRD+ triple-negative breast cancer (TNBC);
- Cohort 3: HRD+ metastatic castration-resistant prostate cancer (mCRPC);
- Cohort 4: Extensive Stage Small Cell Lung Cancer;
- Cohort 5: Gastric/Gastroesophageal Junction Cancer; and
- Cohort 6: patients who have HRD+ nonsquamous non-small cell lung cancer (NSCLC), squamous NSCLC, esophageal cancer, squamous head and neck cancer or soft-tissue sarcomas. Enrollment into these cohorts will occur simultaneously and independently.

For the interim clinical study report (CSR), only cohort 1 to 5 will be included. All cohorts will be included in the final CSR.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

- To determine the safety and tolerability of pamiparib (also known as BGB-290) when given orally in combination with temozolomide (TMZ) (pulsed and continuous)
- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) for pamiparib combined with TMZ (pulsed and continuous)
- To select the recommended Phase 2 dose (RP2D) and schedule of pamiparib in combination with TMZ
- To determine the preliminary antitumor activity of pamiparib in combination with TMZ

3.2 SECONDARY OBJECTIVES

- To characterize the PK of BGB-290 and TMZ

3.3 EXPLORATORY OBJECTIVES

- To evaluate candidate biomarkers in tumor tissue and in peripheral circulation as potential makers of response, resistance, or disease progression

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

- Escalation: Incidence and nature of DLTs
- Escalation and Expansion: Incidence, nature, and severity of AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE) v.4.03 and
- Objective response rate (ORR), as assessed using RECIST v1.1

4.2 SECONDARY ENDPOINTS

- Pharmacokinetic parameters of BGB-290 and TMZ, including but not limited to C_{trough}
- Time-to event- endpoints: e.g., duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)

4.3 EXPLORATORY ENDPOINTS

- Candidate predictive biomarkers, including, but not limited to, expression and mutations of genes in the DNA damage response pathway, and relationship to efficacy and resistance

5 SAMPLE SIZE CONSIDERATIONS

It is expected that approximately 250 patients will be enrolled in the entire study.

- **Dose Escalation Phase:** Approximately 50 patients may be enrolled. More patients may be enrolled if additional doses/schedules are to be evaluated based on emerging data.

- **Dose Expansion Phase:** Approximately 200 patients in total will be treated in 6 cohorts. Each cohort will enroll approximately 20-25 patients each and will be evaluated separately. Cohorts can be closed due to futility or clinical efficacy based on statistical evaluation or due to insufficient patient recruitment. Cohorts can be also further expanded based on emerging data.

  A sample size of 20-25 patients in an expansion cohort will provide the half width of the 90% confidence interval of the ORR approximately 13% to 20% when the observed ORR is approximately 40%. Hence, the low bound is above 20%. This is considered adequate in the preliminary assessment of anticancer activity of pamiparib and TMZ combination therapy. The following Table 1 gives the 90% confidence interval for estimated objective response rate between 36% to 41% for different sample sizes.

Table 1 Estimated Objective Response Rate and 90% Confidence Interval for 20-25 Patients

Sample Size	No. of Responders	Response Rate	90% Confidence Interval	
			Lower Limit	Upper Limit
20	8	40%	22%	61%
21	8	38%	21%	58%
	9	43%	24%	63%
22	8	36%	20%	56%
	9	41%	23%	60%
23	9	39%	22%	58%
	10	43%	26%	62%
24	9	38%	21%	56%
	10	42%	25%	60%
25	10	40%	24%	58%

6 STATISTICAL METHODS

No formal hypothesis testing will be conducted in this study. Data will be described mainly using descriptive statistics. Confidence intervals will be constructed to describe the precision of the point estimates of interest (e.g., objective response rate and disease control rate). Efficacy and safety analyses will be performed by dose escalation and dose expansion phases accordingly. Within dose escalation phase, data will be summarized by dose level within a dosing cohort or all combined. Within dose expansion phase, data will be summarized by cohort.

6.1 ANALYSIS POPULATIONS

- Safety Analysis Set (SAF): includes all patients enrolled into the study who receive any dose of pamiparib and/or TMZ. The Safety Analysis Set will be used for overall survival analysis and safety analyses.
- Efficacy-Evaluable Analysis Set: includes patients in the SAF who had evaluable disease in the dose escalation phase (or measurable disease in the dose expansion phase) at baseline and had at least one postbaseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

  Evaluable disease means patients may have measurable (target lesions) or non-measurable lesions (non-target lesions); measurable disease means patients must have at least 1 measurable lesion (target lesions) and may or may not have non measurable lesions (non-target lesions).
- DLT Evaluable Analysis Set: includes patients who received ≥ 70% of BGB-290 and TMZ during the DLT assessment window (Cycle 1). Additionally, patients who had a DLT event during the DLT assessment window despite receiving < 70% of the scheduled dose will also be included.
- PK Analysis Set: includes patients who received any dose of BGB-290 or TMZ, and contributed at least one plasma concentration.

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 combination treatment of BGB-290 and TMZ (e.g., Cycle 1 Day 1). For assessments conducted on or after the date of the first combination treatment, study day will be calculated as (assessment date – date of first dose of combination treatment + 1). For BGB-290 PK intensive group, BGB-290 is administered starting from 2 days prior to Cycle 1 Day 1 and noted as Study Day -2. For this group, study day will still be calculated from Cycle 1 Day 1 when both BGB-290 and TMZ are administered. 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 per different dosing scheme of BGB-290 and TMZ. Refer to Section 0for more detail.

Treatment-emergent period: The treatment-emergent period is defined as the period of time from the date of the first dose of either pamiparib or TMZ through 30 days after the last dose of pamiparib (permanent discontinuation of pamiparib) or initiation of new anti-cancer therapy. The treatment-emergent period will be used in the summaries of treatment-emergent adverse events (TEAEs) and concomitant medications.

TEAE: An AE started or worsened during the treatment-emergent period. Treatment-related SAEs occurred after treatment-emergent period will also be counted as TEAEs.

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

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.
- 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'.
- Duration of imaging-based event endpoints (such as PFS) 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). For PK analysis, both geometric mean and geometric CV will be included.
- For discrete endpoints, summary statistics will include frequencies and percentages.

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

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.

When summarizing categorical variables, patients with missing data are included in the denominator to calculate percentages unless otherwise specified. When needed, the category of "Missing" is created and the number of patients with missing data is presented.

When summarizing continuous variables, patients with missing data are not included in calculations. No imputations are made.

6.2.4 Multiplicity Adjustment

No multiplicity adjustments will be made in this study. Two-sided 90% confidence interval (CI) will be used to describe the precision of the rate estimate whenever appropriate.

6.2.5 Patient Disposition

The following patient disposition information will be summarized:

- Number of patients treated
- Number (%) of treated patients who discontinued from treatment
- Reason(s) for treatment discontinuation
- Number (%) of treated patients who discontinued from study
- Reason(s) for study discontinuation
- Number (%) of treated patients who remain in study
- Study follow-up time: defined as the time from the first dose date to death date or end of study date (whichever occurred first) for patients who discontinued study or the data cutoff date for ongoing patient

6.2.6 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 the SAF. Also a listing of Covid-19 related protocol deviations will be summarized if applicable.

6.2.7 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics including following variables will be summarized using descriptive statistics:

- Age (years) and age group (years) as < 65, ≥ 65
- Gender
- Race
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Ethnicity
- Tobacco use
- Height
- Weight

6.2.8 Disease History

The number (percentage) of subjects reporting a history of disease and characteristic, as recorded on the eCRF, will be summarized in the SAF. Disease characteristics include time from initial diagnosis to study entry, type of solid tumor (if applicable), locations of metastases, MSI-H mutation, hormone status, tumor histology/cytology, Germline BRCA mutation, somatic BRCA mutation and HRD status.

A subject data listing of disease history will be provided.

6.2.9 Prior Anti-Cancer Systemic Therapies

The number of patients with prior anticancer surgeries, prior systemic therapies, prior radiation therapies will be summarized by cohort and all patients for the SAF. The therapies and surgeries with the same sequence/regimen number are counted as one prior therapy/surgery.

A subject data listing of prior anticancer drug therapies, prior anticancer surgeries and prior radiation therapies will be provided.

6.2.10 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes 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 and percentage of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term for the Safety Analysis Set by cohort and overall. Prior medications are defined as medications that started and ended before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after the patient's last dose of pamiparib or initiation of a new anticancer therapy. A listing of prior and concomitant medications will be provided.

6.2.11 Medical History

Medical History will be coded using MedDRA (version 23.0). The number and percentage of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class (SOC) and preferred term (PT) for the Safety Analysis Set by cohort and overall. A listing of medical history will be provided.

6.3 EFFICACY ANALYSIS

6.3.1 Primary Efficacy Endpoints

Escalation:

- Dose-limiting toxicity in the DLT evaluation period will be used to determine the dose and schedule of pamiparib plus TMZ in the expansion cohorts. The DLT events will be listed for patients in the DLT Evaluable Analysis Set.

All phases:

- Incidence, nature, and severity of AEs will be summarized. Refer to Section 6.4.3 for more detail. The outputs for AEs will be summarized in SAF.
- Overall Response Rate (ORR) by investigator

  Tumor status evaluation including response and progression will be assessed using RECIST v1.1 by investigator throughout this study. This criterion will be used to calculate rumor assessment endpoints including ORR, DCR, DOR and PFS.

  ORR is defined as the proportion of subjects who have a best overall response (BOR) of complete response (CR) or partial response (PR), where BOR is defined as the best response recorded from the first postbaseline tumor assessment until data cutoff date, disease progression or start of new anticancer treatment. For a confirmed ORR, confirmation of CR or PR at next tumor scan (at least 4 weeks from initial documentation) is required.

  Two-sided binomial exact 90% confidence intervals (CI) of ORR will also be constructed for the statistical inference of the point estimate in each cohort.

Tables for confirmed and nonconfirmed ORR will be summarized in Efficacy Evaluable Analysis Set. In addition, a listing of the tumor assessment data in SAF will also be provided. Patients without evaluable postbaseline tumor assessment will be considered as non-responders in the safety analysis set. Maximum tumor shrinkage per patient will be presented in waterfall plots.

6.3.2 Secondary Efficacy Endpoints

- Pharmacokinetic parameters of BGB-290 and TMZ, including but not limited to C_{trough}
  Refer to Section 6.3.6 for more detail.

- Disease Control Rate (DCR) by investigator

  DCR is defined as the proportion of subjects with BOR of CR, PR, or stable disease (SD). Similar to ORR, two-sided binomial exact 90% confidence intervals will be calculated for DCR in each cohort. The table for DCR will be summarized in both SAF and Efficacy Evaluable Analysis Set. Patients without evaluable postbaseline tumor assessment will be considered as non-responders in the safety analysis set.

- Duration of Response (DOR) by investigator

  DOR is defined as the time (month) from the date of the earliest documented CR or PR (that is subsequently confirmed) to disease progression or death due to any cause, whichever occurs earlier. The tables for confirmed and nonconfirmed DOR will be summarized in efficacy evaluable set and only responders will be included in the DOR calculation.

  Kaplan-Meier method will be used to estimate DOR, and corresponding quartiles (including the median) in the responders. A two-sided 90% CIs of median will be calculated for each cohorts using generalized Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982).

  Censoring rule for DOR will follow PFS censoring rule mentioned in FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). The censoring rules are described in Appendix 10.2.

- PFS and PFS-6m by investigator

  PFS is defined as the time (months) from the date of the first dose of combination treatment to disease progression or death due to any cause, whichever occurs first. The PFS-6m is defined as the percentages of subjects who remain alive and progression-free at 6 months. PFS censoring rules are described in Appendix 10.2. If a patient meets the criteria for more than 1 censoring rule, PFS will be censored at the earliest censoring date. The tables for PFS and PFS-6m will be summarized in Efficacy Evaluable Analysis Set.

Kaplan-Meier method will be used to estimate PFS and PFS-6m, and corresponding quartiles (including the median) in the responders. A two-sided 90% CIs of median, Q1 and Q3 will be calculated for each cohorts using generalized Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982). Event free rate at the specified time point (e.g., 3, 6, 9 or 12 months) will be estimated using the Kaplan-Meier method along with the corresponding 90% CI constructed using Greenwood's formula.

- OS and OS-6m
  OS is defined as the time (months) from the date of the first dose of combination treatment to death due to any cause. Deaths that occur on or before the data cutoff date will be considered as an event. Data from patients who are alive on or before the data cutoff date will be censored at the last known alive date. The OS-6m is defined as the percentages of subjects in the analysis population who remain alive and progression-free at 6 months. The tables for OS and OS-6m will be summarized in SAF.

  Kaplan-Meier method will be used to estimate OS and OS-6m, and corresponding quartiles (including the median) in the responders. A two-sided 90% CIs of median, Q1 and Q3 will be calculated for each cohorts using generalized Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982). Event free rate at the specified time point (e.g., 3, 6, 9 or 12 months) will be estimated using the Kaplan-Meier method along with the corresponding 90% CI constructed using Greenwood's formula.

6.3.3 Subgroup Analyses

ORR and DCR will be summarized for patients with SCLC in the expansion stage in subgroups of

- chemosensitivity
- number of prior regimens for advanced or metastatic disease (1, ≥ 2)

6.3.4 CA-125 Assessment

For subjects with ovarian cancer, the CA-125 assessment result including elevated/normal and change from baseline (%) will be provided for each patient in a listing in SAF.

6.3.5 PSA Assessment

For subjects with prostate cancer, PSA will be evaluated. The PSA assessment result including change from baseline and nadir (%) will be provided for each patient in a listing in SAF.

6.3.6 Pharmacokinetic Endpoints

For subjects in BGB-290 PK intensive group who contributed full PK profiles up to 48 hours postdose of Cycle 1 Day 1, and up to 6 hours on Cycle 1 Day 15, the following PK parameters

will be derived: C_{max}, C_{2h}, T_{max}, $T_{1/2}$, AUC_{0-4h}, AUC_{0-inf} (Day 1), AUC_{last}, apparent clearance CL/F, and Vz/F (Day 1).

For the remaining subjects, PK parameters such as C_{min} will be summarized. Population PK analysis may be carried out to include plasma concentrations from this study in an existing model, and additional PK parameters such as apparent clearance of the drug from plasma (CL/F) and AUC may be derived if supported by data. Population PK analysis may be reported separately from the final CSR.

Trough and/or peak plasma concentrations of TMZ will be summarized and compared with appropriate historical control.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data.

A summary of concentration for pamiparib (sparse and intensive sampling separately) and TMZ, and PK parameters for pamiparib, listings for concentration (pamiparib and TMZ separately) and parameters for pamiparib and figures of concentration vs time for intensive pamiparib PK sampling will be provided.

6.3.7 Exploratory Endpoints

Exploratory endpoints include blood and tumor biomarkers will be analyzed using the SAF. The correlation of predictive biomarkers with efficacy endpoints for study treatment will be explored.

6.4 SAFETY ANALYSES

All safety analyses will be performed by dose level in dose escalation phase and by cohort in dose expansion phase and by total (dose escalation and expansion phases combined). Safety will be assessed by monitoring and recording of all AEs graded by CTCAE v4.03. Laboratory values (hematology, serum chemistry, coagulation, and urinalysis), vital signs, physical exams and ECGs findings will also be used in determining the safety. Patients in SAF will be included for safety analyses.

6.4.1 Extent of Exposure

Extent of exposure to study drug will be summarized descriptively as the duration of exposure (months), cumulative total dose received per subject (mg), actual dose intensity (mg/day), relative dose intensity (%), dose reduction, dose interruption, and dose missed per patient.

Duration of exposure (months) is determined for each patient and study medication based on dosing schedule. For daily dosing of both BGB-290 and TMZ, it will be calculated as (date of last dose – date of first dose + 1)/30.4375. For the dosing schedule of TMZ administered 7 days a cycle, it will be calculated as (date of last dose – date of first dose + 22)/30.4375. For the

dosing schedule of TMZ administered 14 days a cycle, it will be calculated as (date of last dose – date of first dose + 15)/30.4375.
Dose intensity per subject is defined for each study medication as sum of actual dose received divided by duration of treatment. Relative dose intensity is defined as total actual dose received divided by total planned dose.

The number (percentage) of patients who had missed doses, dose reductions and dose interruptions summarized. Frequency of reductions and dose interruptions will be summarized by categories (1, 2, 3, ≥4).

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

6.4.2 Dose Limiting Toxicity

Dose-limiting toxicity in the DLT evaluation period will be used to determine the dose and schedule of BGB-290 plus TMZ in the expansion cohorts. DLTs will be taken from the adverse event eCRF. Number and percentage of patients with DLT events will be listed at each combination dosing level in the DLT evaluable analysis set.

6.4.3 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to MedDRA (Version 23.0) 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 or worsened during the treatment-emergent period (refer to Section 6.2.1). Treatment-related SAEs occurred after treatment-emergent period will also be counted as TEAEs. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with grade 3 or above, and treatment-related SAEs will be provided. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship.

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

The number (percentage) of subjects with treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, and treatment-related SAEs will be summarized by SOC, PT and CTCAE grade. TEAEs with grade 3 or above will also be summarized by PT in descending order. Incidence of TEAEs of interest will be summarized by SOC and PT. TEAEs of interest, if needed, will be defined before database lock.

Subject data listings of all AEs, SAEs, treatment-related AEs, grade 3 or above AEs, AEs that led to death and AEs that led to treatment discontinuation, dose reduction or dose interruption will be provided.

6.4.4 Laboratory Values

Laboratory safety tests will be evaluated for selected parameters.

Laboratory parameters listed in Table 2 will be graded in NCI CTCAE v4.03. A shift table (baseline grade to maximum grade after dosing on Cycle 1 Day 1) will be provided for hemoglobin, platelet count, white blood cell count, neutrophil and lymphocyte. Patient data listings of selected hematology and serum chemistry parameters, urinalysis and coagulation will be provided.

Table 2 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)
Blood Urea Nitrogen	Monocyte (Absolute)
Creatinine	Basophil (Absolute)
Sodium	Eosinophil (Absolute)
Phosphate	
Glucose	
Lactate dehydrogenase	
Total Protein	
Potassium	

6.4.5 Vital Signs

Vital sign parameters (systolic and diastolic blood pressure [BP], temperature, height and weight) will be listed by subjects and visits.

6.4.6 Electrocardiograms

During the BGB-290 PK intensive period (Day -2) and cycle 1, ECGs will be performed in triplicate on a machine provided by the sponsor. ECG findings at baseline, postbaseline will be listed by visit and/or time point. In addition, single ECG and abnormal QT interval with Fridericia's correction (QTcF) derived from triplicate ECG will also be listed.

6.4.7 ECOG Performance Status

ECOG scores and change from baseline will be listed by visit for the SAF.

7 INTERIM ANALYSIS

In dose escalation phase, before the dose is escalated to the next level, the safety review team will review the safety data to determine the next dose level. The recommended dose for dose expansion phase will be determined by the safety review team before the dose expansion phase.

Interim CSR may be conducted for the purpose of safety and/or efficacy review.

8 CHANGES IN THE PLANNED ANALYSIS

There are some changed in the planned analysis and they are listed below:

- DLT will be provided in a listing and no descriptive statistics will be provided.
- Subgroup analysis for ORR will only be done for SCLC patients in chemosensitivity and number of prior regimens.
- All by-visit analyses will be removed, and the following will be performed: hematology data will be presented in a shift table and serum chemistry will be provided in a listing. ECG will be listed. A listing of QTcF will be provided for patients with abnormal postbaseline values and abnormal changes from baseline. ECOG and vital signs will be provided in listings.
- Ninety percent CIs will be presented instead of 95% CIs**.**
- OS analyses will be conducted in SAF instead of Efficacy Evaluable Analysis Set**.** Only PFS and OS analyses will be conducted and not PFS-6m and OS-6m analyses.
- Efficacy analyses such as ORR, PFS and DOR will be based on radiographic responses or radiographic progression.
- Treatment-emergent SAEs, treatment-related TEAEs, TEAEs with grade 3 or above, and treatment-related SAEs will be summarized by SOC, PT and CTCAE grade. AEs that led

to death and AEs that led to treatment discontinuation, dose reduction or dose interruption will only be listed.

- Number of treatment cycles will not be summarized. Instead, reasons for dose reduction, dose interruption and missed dose will be summarized.

9 REFERENCES

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10 APPENDICES

10.1 HANDLING MISSING DATE INFORMATION

In general, missing or partial dates will not be imputed at data level. The following rules will apply for the specific analysis and summary purposes mentioned below only.

10.1.1 Prior/Concomitant Medications, Disease and Medical History, Prior Therapy (Drug, Surgery/Procedure, Radiotherapy)

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 missing or partial dates for medications /therapy/procedure:

	Missing	Impute	Exception
Start Date	Day	01	N/A
	Day/Month	January 01	N/A
	Day/Month/Year or Year only	Do not impute	N/A
End Date	Day	Last day of the month	N/A
	Day/Month	December 31	N/A
	Day/Month/Year or Year only	Do not impute	N/A

If the imputed start date becomes after end date, then update start date same as end date. And if the imputed start date or end date becomes after death date, then set to death date.

For disease history, medical history and prior therapy, including initial diagnosis date, therapy date (start/end date), or surgery date, if the imputed start date or end date becomes after first dose date, then set to first dose date - 1.

10.1.2 Initial Diagnosis and Most Recent Progression

For initial diagnosis date and most recent progression date, which has no duration and only start date is available, impute the date using the following rule:

	Missing	Impute	Exception
Initial Diagnosis Date/ Most Recent Progression Date	Day	01	N/A
	Day/Month	January 01	N/A
	Day/Month/Year or Year only	Do not impute	N/A

If the imputed initial diagnosis date or most recent progression date is on or after the treatment start date, then set to treatment start date - 1.

10.1.3 Adverse Events

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 missing or partial dates for adverse events:

	Missing	Impute	Exception
Start Date	Day	01	If Month and Year = Month and Year of treatment start date, then set to treatment start date
	Day / Month	January 01	If Year = Year of treatment start date, then set to treatment start date
	Day / Month / Year or Year only	Do not impute	If AE End Date > treatment start date, then set to treatment start date

End Date	Day	Last day of the month	N/A
	Day / Month	December 31	N/A
	Day / Month / Year or Year only	Do not impute	N/A

If the imputed AE start date becomes after AE end date, then update AE start date same as AE end date. And if the imputed start date or end date becomes after death date, then set to death date.

The following rule will be applied to impute missing toxicity grade of AE:

1. The highest grade will be used from patient's AEs with the same preferred term.
2. If patient has no AEs with the same preferred terms, the highest grade of the AEs with the same SOC will be used.
3. If patient has no same SOC, the highest grade of all AEs from that patient will be used.
4. If it is the single AE reported for that patient, no imputation for the missing grade will be done.

10.1.4 Deaths

In case complete death dates are not recorded, impute as follows:

- If year, month and day are all missing, then impute the death date as the last date of patient known to be alive + 1 for efficacy analyses, e.g., DOR, PFS and OS.
- If both month and day are missing, then the imputed month and day will be 01Jan or the last date of the last date of patient known to be alive + 1, whichever is later.
- If only day is missing, the death will be assumed to be on the first day of the month or the last date of patient known to be alive + 1, whichever is later.

10.1.5 New Anticancer therapy

If the start day of a subsequent anticancer therapy is incomplete or missing, impute as follows:

- if both month and day are missing,
    1) impute the date as 31Dec, if the year is earlier than the year of the first PD date + 1 or the treatment end date + 1, whichever is later
    2) impute the date as 01Jan, if the year is later than the year of the first PD date or the treatment end date + 1, whichever is later

3) impute the date as the first PD date + 1 or the treatment end date + 1, whichever is later, if the year is the same year of first PD date + 1 or the treatment end date + 1, whichever is later

- if only day is missing,

4) impute the date as the first day of the month if year and month are available and partial new anticancer therapy date still could indicate it is at least one month later than the first PD date +1 or the treatment end date +1, whichever is later.

5) impute the date as the last day of the month if year and month are available and partial new anticancer therapy date still could indicate it is at least one month earlier than the first PD date +1 or the treatment end date +1, whichever is later.

6) Impute the date as the first PD date +1 or the treatment end date +1, whichever is later, if the year and month are the same year and month of first PD date +1 or the treatment end date +1, whichever is later.

- The treatment end date refers to the last dose date of pamiparib.

10.2 CENSORING RULES

Table 3 shows the primary censoring rules for the derivation of PFS.

Table 3 Censoring Rules for Analysis of PFS

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments or no post baseline tumor assessment	Reference start date (e.g., C1D1)	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 PD after two or more consecutive missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

9	A patient meets the criteria for more than 1 censoring rules above	Date of the earliest censoring date among all events	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 or by IRC.

**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, which is 17 weeks (119 days).