STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-290-303
Study Protocol Title:	A Phase 2, Double-blind, Randomized Study of BGB-290 versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
CI	confidence interval
CR	complete response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire
EORTC QLQ-STO22	European Organisation for Research and Treatment of Cancer Quality of Life gastric cancer module
EOT	end of treatment
EQ-5D-5L	European Quality of Life 5-Dimensions 5-Levels Health Questionnaire
HR	hazard ratio
HRD	homologous recombination deficiency
ITT	Intent-to-Treat
LOH	loss of heterozygosity
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
SAE	serious adverse event
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TSST	Time from randomization to second subsequent anticancer therapy or death
ULN	upper limit of normal

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 Protocol BGB-290-303: A Phase 2, Double-blind, Randomized Study of BGB-290 (pamiparib) versus Placebo as Maintenance Therapy in Patients with Inoperable Locally Advanced or Metastatic Gastric Cancer that Responded to Platinum-based First-line Chemotherapy. The focus of this SAP is for the planned final analysis specified in the study protocol.

Reference materials for this statistical plan include the protocol BGB-290-303 (version 1.0, 2020-02-13). 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. The SAP will be finalized and approved before database lock for the primary analysis of this study. Statistical programming may occur in a blinded manner as study data accumulate to have analysis programs ready at the time of database lock.

2 STUDY OVERVIEW

This is a double-blind, placebo-controlled, randomized, multicenter, global Phase 2 study comparing the efficacy and safety of single-agent poly (ADP-ribose) polymerase (PARP) inhibitor pamiparib to placebo as maintenance therapy in patients with advanced gastric cancer who have completed first-line platinum-based chemotherapy.

To be eligible for participation in the study, patients must have histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction with inoperable locally advanced or metastatic disease. Patients must have achieved a partial response (PR) that is maintained for ≥ 4 weeks or complete response (CR) as determined by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 with platinum-based first-line chemotherapy.

All patients will be randomized within 8 weeks after the last platinum dose of first-line chemotherapy. Central interactive response technology will be used to randomize patients in a 1:1 ratio and assign eligible patients to 1 of 2 arms: Arm A – pamiparib or Arm B – Placebo. Patient randomization will be stratified by:

- HRD status (LOH_{high} versus LOH_{low} versus unknown)
- Region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus rest of world [ROW])

- Eastern Cooperative Oncology Group (ECOG) performance status (0 versus 1)

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

- To evaluate the efficacy of maintenance therapy with pamiparib versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a CR or confirmed PR after first-line platinum-based chemotherapy, as measured by:
  - Progression-free survival (PFS) by RECIST Version 1.1 by investigator assessment

3.2 SECONDARY OBJECTIVES

- To further evaluate the efficacy of maintenance therapy with pamiparib versus placebo in patients with inoperable locally advanced or metastatic gastric cancer with a CR or confirmed PR after first-line platinum-based chemotherapy, as measured by:
  - Overall survival (OS)
  - Time to second subsequent treatment (TSST)
  - Objective response rate (ORR; CR or PR) by investigator assessment
  - Duration of response (DOR) by investigator assessment
  - Time to response by investigator assessment
- To evaluate safety and tolerability of pamiparib versus placebo, as measured by:
  - Incidence, timing, and severity of treatment-emergent adverse events (TEAEs), graded according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03 or higher

3.3 EXPLORATORY OBJECTIVES

- To confirm the PK of pamiparib, as measured by:
  - Lowest observed plasma concentrations (C_{trough}) at steady-state and plasma concentration two hours post-dose (C_{2h}) after a single dose and at steady-state for patients who received pamiparib
- To assess patient-reported outcomes on health-related quality of life, as measured by:
  - European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
  - European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30)
  - EORTC QLQ gastric cancer module (EORTC QLQ-STO22)

- To explore potential biomarkers associated with the pharmacodynamics, response, and resistance to pamiparib:
    - Including, but not limited to, expression and mutations of genes in the DNA damage response pathway, LOH, and relationship to efficacy and resistance to pamiparib

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

PFS, defined as the time from randomization to progressive disease (PD) per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever occurs first.

4.2 SECONDARY ENDPOINTS

Efficacy assessment:

- OS, defined as the time from randomization to death due to any cause
- Time to second subsequent treatment (TSST), defined as the time from randomization until the second subsequent anticancer therapy or death after next-line therapy
- ORR, defined as the proportion of patients with a best overall response of CR or PR per RECIST Version 1.1 by investigator assessment
- DOR, defined as the time from the first documented confirmed response of CR or PR to PD per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever occurs first
- Time to response, defined as the time from randomization to the first documented response of CR or PR per RECIST Version 1.1 by investigator assessment

Safety assessment:

- Incidence, timing, and severity of TEAEs, graded according to NCI-CTCAE Version 4.03 or higher
- Safety and tolerability assessment of laboratory measurements, vital signs, and ECG findings

4.3 EXPLORATORY ENDPOINTS

Pharmacokinetics (PK) assessment:

- Lowest observed plasma concentrations (C_{trough}) at steady-state for patients who received pamiparib

Patient reported outcomes (PRO) assessments:

- European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
- European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30)
- EORTC QLQ gastric cancer module (EORTC QLQ-STO22)

Biomarkers assessment associated with the pharmacodynamics, response, and resistance to pamiparib:

- Including, but not limited to, expression and mutations of genes in the DNA damage response pathway, LOH, and relationship to efficacy and resistance to pamiparib

5 SAMPLE SIZE CONSIDERATIONS

This study is designed to provide 80% power for PFS. The following assumptions are used in determining the sample size for this study:

- Overall type I error rate: 0.1 (1-sided)
- Randomization: 1:1
- Median PFS for placebo group: 6.0 months
- PFS hazard ratio (HR; pamiparib/placebo): 0.63

A sample size of approximately 128 patients (64 per treatment group) is required to achieve 85 PFS events within the planned study duration of approximately 26 months after the first patient is randomized to study, assuming an estimated accrual period of 20 months.

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

Intent-to-Treat (ITT) Analysis Set includes all randomized patients who are assigned to study treatment (pamiparib or placebo). The ITT Analysis Set will be used for all efficacy analyses, except for endpoints ORR, DOR and time to response.

Safety Analysis Set includes all patients in the ITT Analysis Set who receive at least one dose of study treatment (pamiparib or placebo). The Safety Analysis Set will be used for all safety analyses.

Efficacy Evaluable Analysis Set includes all randomized patients who had measurable disease at baseline and had at least one post baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment. The Efficacy Evaluable Analysis Set will be used for all efficacy analyses related to ORR, DOR and time to response by investigator assessment.

PK Analysis Set includes all patients who received pamiparib 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 randomization date for efficacy analysis, and date of the first dose of study treatment for safety analysis. For assessments conducted on or after the randomization date or date of the first dose of study treatment, study day will be calculated as (assessment date – randomization date or date of first dose of study treatment + 1). For assessments conducted before the randomization date or date of the first dose of study treatment, study day is calculated as (assessment date – randomization date or date of first dose of study treatment). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 10.1.

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

Baseline: Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the time of first dose date. The baseline tumor assessment is defined as the screening assessment in reference to randomization date.

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 the nearest tenth (.1) unless otherwise specified.
- 1 month = 30.4375 days. Number of months is calculated as (days / 30.4375) rounded up to the nearest tenth (.1) unless otherwise specified.
- 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 (the median of the lower half of the data), Q3 (the median of the upper half of the data) and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events, concomitant medications, disease history, and prior therapy. 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 as captured in electrical data base, 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 primary 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

Adjustments for stratification factors (region, ECOG performance status) as covariates are planned for primary and secondary analyses in the study. Baseline characteristics may be used in the model as additional covariates as supportive exploratory analyses, if deemed necessary.

6.2.5 Multiplicity Adjustment

No multiplicity adjustment is considered in this study.

6.2.6 Data Integrity

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

6.3 PATIENT CHARACTERISTICS

6.3.1 Patient Disposition

The following patient disposition information will be summarized by treatment groups in the ITT Analysis Set:

- Number of randomized patients
- Number of treated patients
- Number (percentage) of treated patients who discontinued treatment
- Reason for treatment discontinuation
- Number (percentage) of treated patients who discontinued study (including those who discontinued study treatment and did not enter survival follow-up, and those discontinued from the survival follow-up)
- Reason for study discontinuation
- Duration of follow-up

The primary reason for study treatment and study discontinued will be summarized according to the categories in the electronic case report form.

Survival status (alive, deceased, withdrew consent, lost to follow-up, or unknown) at the data cutoff date will be listed using the data from the survival follow-ups.

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 ITT Analysis Set. They will also be listed by each category.

6.3.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics for patients in the ITT Analysis Set:

- Age (years) and age categorized (years) as < 65, ≥ 65
- Gender
- Race
- Ethnicity
- Height (cm) and weight (kg)
- Body mass index (BMI in kg/m^2)

- Eastern Cooperative Oncology Group (ECOG) performance status

A listing of demographic and baseline characteristics for patients in the ITT Analysis Set will be provided.

6.3.4 Disease History

The number (percentage) of patients reporting a history of disease and characteristic, as recorded on the CRF, will be summarized for patients in the ITT Analysis Set. The following will be included for disease history and characteristics:

- Primary location/types of solid tumor
- Solid tumor staging
- Time since initial diagnosis, defined as date of first dose of study treatment minus date of initial diagnosis
- Histologic grade
- Metastatic disease location

A listing of disease history and characteristics for patients in the ITT Analysis Set will be provided.

6.3.5 Prior Anticancer Drug Therapies and Radiotherapy

The number and percentage of patients with prior anticancer drug therapies, number of prior regimen, duration of last therapy, best overall response for last therapy, reason that last therapy ended, time from end of last therapy to study entry, treatment setting for last therapy, and name and/or type of drug will be summarized for patients treated in the ITT Analysis Set.

The number and percentage of patients with any prior anticancer radiotherapy, number of all prior radiotherapy treatments, intent and setting of therapy, site irradiated, time from end of last radiotherapy to study entry, and duration of last therapy will be summarized for patients treated in the ITT Analysis Set.

The therapies with the same sequence/regimen number are counted as one prior therapy. Previous anticancer medication will be summarized in WHO DD preferred term.

A listing of prior anticancer drug therapies and radiotherapy in the ITT Analysis Set will be provided.

6.3.6 Medical History

Medical History will be coded using MedDRA Version 22 or higher. 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 ITT Analysis Set. A listing of medical history will be provided.

6.3.7 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 (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term in the ITT Analysis Set. 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 or initiation of a new anticancer therapy. A listing of prior and concomitant medications will be provided.

6.3.8 Procedure or Surgery

The number and percentage of patients with any procedure or surgery, name of procedure or surgeries, and reason for procedure or surgery will be summarized for patients treated in the ITT Analysis Set.

A listing of procedure or surgery for patients in the ITT Analysis Set will be provided.

6.3.9 Post Treatment Anticancer Drug Therapy

The number and percentage of patients with post-treatment anticancer drug therapies, number of post treatment regimen, time to first post treatment therapy, best overall response for therapy, name of medication, and duration of post treatment therapy will be summarized for patients treated in the ITT Analysis Set.

The therapies with the same sequence/regimen number are counted as one post-treatment therapy. Post treatment anticancer medication will be summarized in WHO DD preferred term.

A listing of post treatment anticancer therapy for patients in the ITT Analysis Set will be provided.

6.4 EFFICACY ANALYSIS

6.4.1 Primary Efficacy Analysis

Progression-Free Survival (PFS)

PFS is defined as the time from randomization date to disease progression per RECIST Version 1.1 by investigator assessment or death, whichever occurs first.

The final PFS analysis will be performed when 85 PFS events have occurred. The final PFS analysis will include all PFS events up to the date of data cutoff which is pre-defined based on the projected 85 PFS events on the blinded manner. A stratified 1-sided log-rank test at a 0.1 significance level incorporating the randomized stratification factors will be used to compare the distribution of PFS between pamiparib (Arm A) and placebo (Arm B).

The null and alternative hypotheses for the final PFS analysis are as follows:

H_0: hazard ratio [HR] (pamiparib/placebo) = 1

Ha: hazard ratio [HR] (pamiparib/placebo) < 1

The treatment effect will be estimated by fitting a Cox Proportional Hazards model to the PFS including treatment arm as a factor and stratification factors (region, ECOG performance status) as strata. From this model, the HR will be estimated and presented with a 2-sided 95% CI.

The median and other quartiles of PFS for each treatment group will be estimated using the Kaplan-Meier method, and the 2-sided 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). The point estimate of PFS rates and the corresponding 95% CIs at selected landmark points (every three months up to 24 months) will be provided based on the Greenwood's estimate of the variance (Greenwood 1926). Kaplan-Meier curves for PFS will also be generated and plotted over time to provide a visual description of the PFS change over time. Primary efficacy analysis will be conducted by using the ITT Analysis Set.

PFS censoring rule will follow FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2007). Data for patients without PD per RECIST Version 1.1 or death at the time of analysis will be censored at the date of the last tumor assessment. Data for patients who are lost to follow-up before documented PD will be censored at the last tumor assessment date when the patient is known to be progression-free. Data for patients who started new anticancer therapy will be censored at the last tumor assessment date before the introduction of new anticancer therapy. Data for patients who had 2 or more consecutive missed scheduled tumor assessments immediately before PD or death will be censored at the last tumor assessment date before the 2 missed tumor assessments.

Table 1 shows the primary censoring rules for the derivation of PFS using RECIST 1.1 criteria based upon investigator's tumor assessment.

Table 1. Censoring Rules for Analysis of Progression-Free Survival Per RECIST 1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or postbaseline tumor assessments	Randomization 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 cut-off or withdrawal from study	Date of last adequate radiologic assessment before or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last radiologic assessment before or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after immediate more than one 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 17 weeks (eg, 16 week + 1 week).

6.4.2 Secondary Efficacy Analysis

Overall Survival (OS)

OS is the key secondary efficacy endpoint and is defined as the time from randomization to death due to any cause.

A stratified log-rank test incorporating the randomized stratification factors (region, ECOG performance status) will be used to compare treatment groups. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median and other quartiles of OS for each treatment group will be estimated using the Kaplan-Meier method and the 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). Kaplan-Meier curves for OS will also be generated and plotted over time to provide a visual description of the OS change over time.

OS data will be censored at the date that the patient was last known to be alive before the date of data cutoff. For patient who died and have last known alive date after the date of data cutoff, OS data will be censored at the date of data cutoff. Analysis will be conducted by using the ITT Analysis Set.

Time to second subsequent treatment (TSST)

TSST is defined as the time from randomization until the second subsequent anticancer therapy or death. The second subsequent anicancer therapy should be conditional on the first anticancer therapy and on or after date of PD from the first anticancer therapy. Patients alive and without the second anticancer therapy, or alive with the second anticancer therapy but no PD from the first anticancer therapy will be censored at last known alive. Details of the censoring rule are specified in Table 2.

If data collected is deemed as suffice, TSST will be assessed using a stratified log-rank test incorporating the randomized stratification factors (region, ECOG performance status) in ITT Analysis Set. The HR and its 2-sided 95% CI will be estimated using the stratified Cox-proportional hazards model. The median and other quartiles of TSST for each treatment group will be estimated using the Kaplan-Meier method and the 95% CI will be calculated using the Brookmeyer-Crowley method (Brookmeyer and Crowley, 1982). Analysis will be conducted by using the ITT Analysis Set.

Table 2. Censoring Rules for Analysis of TSST

No.	Situation	Date of Progression or Censoring	Outcome
1	Death	Death Date	Event
2	Second subsequent anticancer therapy	Second subsequent anticancer therapy start date	Event
3	No event of interest when analysis	Last available date from the following for patient with EOT: 1) EOT date 2) Last long-term followup visit date 3) Post-treatment anticancer treatment date Or cutoff date for patient on treatment	Censored

Objective Response Rate (ORR) by investigator assessment

ORR is defined as the proportion of patients with a best overall response of CR or PR per RECIST Version 1.1 by investigator assessment for the Efficacy Evaluable Analysis Set, before data cutoff or initiation of the next line of anticancer therapy, whichever comes first. The number and proportion of patients who achieve CR or PR according to both RECIST 1.1 will be summarized. Patients without postbaseline tumor assessment will be considered as non-responders. The ORR and its exact 2-sided 95% CI will be reported for each treatment group. A

Cochran-Mantel-Haenszel score test will be used to compare treatment groups. Confirmation of CR and PR are not required in this randomized study per RECIST v1.1.

The best overall response (BOR) will be summarized by the following categories for the Efficacy Evaluable Analysis Set. Patients without post-baseline disease assessment should be considered non-responders.

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable / Not evaluated

Duration of Response (DOR)

DOR is defined as the time from the first documented confirmed response of CR or PR to PD per RECIST Version 1.1 by investigator assessment or death due to any cause, whichever occurs first. Only patients with CR or PR during the study will be included in duration of response analysis. Censoring rule for DOR will follow PFS censoring rule.

The median and other quartiles of duration of response and its 2-sided 95% CI for each treatment group will be provided. Kaplan-Meier curve will be used to estimate median time and 95% CI for duration of response.

Waterfall plots will be provided for the maximum tumor shrinkage based on target lesion. The maximum tumor shrinkage based on target lesion used in the plots will be listed. These analyses will be performed based on RECIST 1.1.

Time to response by investigator assessment

Time to response is defined as the time from randomization to the first documented confirmed response of CR or PR per RECIST Version 1.1 by investigator assessment. Only patients with CR or PR during the study will be included in time to response analysis. Descriptive statistics will be provided for the Efficacy Evaluable Analysis Set.

6.4.3 Subgroup Analyses

Table and forest plot of subgroup analysis in PFS will be provided based on the following subgroups:

- Geographic region (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea versus ROW)
- EGOG performance status at baseline (0 versus 1)

- Age at baseline: < 65 years versus ≥ 65 years
- Race: White versus Asian versus others

These planned subgroup analyses may not be explored if sufficient number of samples cannot be achieved for certain subgroups.

6.4.4 Exploratory Efficacy Analysis

The scores from these following health-related questionnaires will be summarized by each assessment and treatment descriptively (n [%] for categorical variables):

- European Quality of Life 5-Dimensions 5-Levels Health Questionnaire (EQ-5D-5L)
- European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30)
- EORTC QLQ gastric cancer module (EORTC QLQ-STO22)

The actual scale and the change from baseline to each post-baseline visit and to the end of treatment on overall health in EQ-5D-5L and overall health and quality of life in EORTC QLQ-C30 will be summarized by visit using descriptive summary statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum for continuous variables). A listing of scores from these health-related questionnaires for patients in the ITT Analysis Set will be provided.

6.5 SAFETY ANALYSES

All safety analyses will be performed by cohort and by total (combined cohorts) 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, ECOG and their changes from baseline will be summarized using descriptive statistics (eg, 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 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. The total dose received per patient (mg), which is sum of actual received doses per patient, will also be summarized with descriptive statistics.

Number of patients with dose modification and their reasons, and number of patients with any dose missed, reduced, and increased will be summarized by counts and percentages. In addition, frequency of dose reductions, dose missed, and dose increased will be summarized by categories.

Average dose intensity per patient (in mg/day) and relative dose intensity (total dose received / total dose prescribed) 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 this patient. Relative dose intensity is calculated as the total dose (mg) taken by a patient divided by the total dose prescribed for the patient.

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

6.5.2 Adverse Events

AEs will be graded by the investigators using NCI 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 (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 treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the date of the first dose of study treatment through 30 days after the last dose (permanent discontinuation of study treatment) or initiation of new anticancer 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 table of patients with at least one TEAE will be presented, as the number (percentage), with the incidence of following:

- patients with any TEAE
- patients with any TEAE with Grade 3 or higher
- patients with any serious TEAE
- patients with any TEAE leading to death
- patients with any TEAE leading to treatment discontinuation
- patients with any TEAE leading to dose modification
  - patients with any TEAE leading to dose interruption
  - patients with any TEAE leading to dose reduction
- patients with any treatment-related TEAE
- patients with any treatment-related TEAE with Grade 3 or higher
- patients with any treatment-related serious TEAE

- patients with any treatment-related TEAE leading to death
- patients with any treatment-related TEAE leading to treatment discontinuation
- patients with any treatment-related TEAE leading to dose modification
  - patients with any treatment-related TEAE leading to dose interruption
  - patients with any treatment-related TEAE leading to dose reduction

Summaries of all above TEAEs will also be reported as the number (percentage) of patients by SOC and PT.

Summaries of all TEAEs, SAE, Grade 3 or higher TEAEs, treatment-related TEAEs, and TEAE leading to treatment discontinuation will also be provided by PT only in descending order of frequency.

All TEAEs, SAE, Grade 3 or higher TEAEs, treatment-related TEAEs and TEAEs leading to treatment discontinuation will also be summarized by SOC, PT, and maximum severity. A patient will be counted only once by the highest severity grade according to CTCAE v.4.03 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT.

Patient data listings of all AEs, SAEs, treatment-related AEs, Grade 3 or above AEs, AEs that led to death, AEs that led to treatment discontinuation, and AEs that led to dose modification will be provided.

6.5.3 Death

All deaths and causes of death will be summarized by treatment arm, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment completion/discontinuation. Patient data listings of death will be provided.

6.5.4 Laboratory Values

Laboratory safety tests of serum chemistry and hematology will be evaluated for selected parameters described in Table 3. The actual value and the change from baseline to each post-baseline visit and to the end of treatment will be summarized by visit using descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables).

Urinalysis includes blood, protein, ketones, glucose, red blood cells, and white blood cells. Urinalysis results will not be summarized descriptively 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. Number (percentage) of patients with abnormal postbaseline laboratory values will be summarized.

Patient data listings of selected hematology and serum chemistry parameters, and urinalysis will be provided.

A summary of the liver function test abnormalities will also be presented based on Hy's law laboratory criteria defined as 1) Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) > 3 x ULN, 2) Total bilirubin (TBL) > 2 x ULN and 3) Alkaline phosphatase (ALP) < 2 x ULN and ALP ≥ 2 x ULN for patients with 1) and 2), at any postbaseline visit.

Table 3. Serum Chemistry, Hematology, and Urinalysis Laboratory Tests

Serum Chemistry	Hematology	Urinalysis
Alkaline phosphatase (ALP)	Hemoglobin	Blood
Alanine aminotransferase (ALT)	Platelet counts	Protein
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Ketones
Albumin	Neutrophil	Glucose
Total bilirubin	Lymphocyte	Red blood cells
Blood Urea Nitrogen		White blood cells
Creatinine		
Chloride		
Phosphate		
Glucose		
Lactate dehydrogenase		
Total Protein		
Potassium		
Sodium		

6.5.5 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature, and weight) and changes from baseline will be presented by visit. Vital signs will be listed by patients and visits.

6.5.6 Electrocardiograms (ECG)

ECG will be obtained during screening, predose and 2 hours postdose on Cycle 1 Day 1 and Cycle 1 Day 15, and end of treatment (EOT). Additional ECGs may be performed as clinically

indicated at other timepoints. ECG findings at baseline and all other predose and postdose assessments on the first cycle and EOT will be descriptively summarized.

The number and percentage of patients satisfying the following QTcF conditions at any time post-baseline will be summarized:

- 450, > 480, or > 500 msec
- ≤ 30 msec increase from baseline, > 30 and ≤ 60 msec increase from baseline, or > 60 msec increase from baseline

Patient listing of ECG will be provided for all ECG recordings with the indicator whether the abnormality is clinical significance. For patients without QTcF, all measures in QTcB will be transformed into QTcF by standard derivation method in summary tables.

6.5.7 Eastern Cooperative Oncology Group (ECOG)

ECOG scores will be summarized by visit using descriptive statistics for Safety Analysis Set.

6.6 PHARMACOKINETIC ANALYSES

Individual and summary plasma concentration of pamiparib will be presented.

PLASMA CONCENTRATIONS

PK samples will be collected from patients at predose (within 30 minutes before dose) and 2 hours (±30 minutes) postdose on Cycle 1 Day 1 and Cycle 1 Day 15. PK sampling will be collected only at sites that have the capability to collect PK samples. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the study manual. PK samples collected from patients assigned to placebo treatment will not be analyzed for pamiparib concentrations.

Plasma pamiparib concentration-time data will be summarized in tabular form. Pharmacokinetic concentration data for pamiparib will be listed including the dose level, relative time to dosing, actual sample collection time. The concentration data will also be summarized with descriptive statistics for each timepoint. The number of patients with non-missing plasma concentration, mean, standard deviation, minimum, median, maximum, geometric coefficient of variation and geometric mean will be included in the summary.

6.7 PHARMACODYNAMIC ANALYSES

Correlative biomarker analyses in tumor tissues and blood will be performed. A separate statistical analysis plan will outline details of the biomarker analyses.

7 INTERIM ANALYSIS

No interim analysis is considered in this study.

8 CHANGES IN THE PLANNED ANALYSIS

- The Per-Protocol (PP) analysis set defined in the protocol BGB-290-303 (version 1.0, 2020-02-13) will not be considered in the analysis.
- Progression-free survival 2 (PFS2) by investigator assessment as secondary efficacy endpoints defined in the protocol BGB-290-303 (version 1.0, 2020-02-13) will not be considered in the analysis.
- Confirmation of response will not be required for ORR in randomized clinical studies per RECIST v1.1. No confirmation of response required for the analysis of DOR and Time to response to be consistent with analysis of ORR.
- The stratification factor of HRD status (LOH_{high} versus LOH_{low} versus unknown) will not be included as strata for PFS, OS, and TSST nor covariate in primary or secondary analyses due to high rate of patients with unknown LOH reported. And the Region will have three strata (China/Hong Kong/Taiwan versus Australia/Europe/North America versus Japan/South Korea/rest of world [ROW]) for PFS, OS, TSST, and covariate in primary or secondary analyses after combining patients in Japan/South Korea with patients in ROW as small number of patients were enrolled in Japan and no patients were enrolled in South Korea.
- No PK parameters will be derived and reported in clinical study report. The definition of PK analysis set is thus modified as all patients who have at least one plasma concentration.

9 REFERENCES

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10 APPENDIX

10.1 HANDLING OF PARTIALLY MISSING DATES

1) 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	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 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.

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

	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

For concomitant medications; if the imputed start date or end date becomes after death date, then set to death date.

For disease history and prior therapy, including initial diagnosis date, relapse 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 - 15.

3) Initial Diagnosis, Metastatic Disease, and Most Recent Progression

	Missing	Impute	Exception
Initial Diagnosis Date/ Metastatic Disease 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, metastatic disease date or most recent progression date is on or after the treatment start date, then set to treatment start date - 1.

4) Death

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

- If both month and day are missing, then the imputed month and day will be 01Jan or 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.

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,
  1) 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.
  2) 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.
  3) 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.

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