BeiGene

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-290-104
Study Protocol Title:	A Phase 1b/2 study to assess the safety, tolerability and efficacy of BGB-290 in combination with radiation therapy and/or temozolomide in subjects with first-line or recurrent/refractory glioblastoma
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
BOR	best overall response
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CTCAE	common Terminology Criteria for Adverse Events
C_{trough}	lowest concentration reached before the next dose administered
DCR	disease control rate
DLT	dose limiting toxicity
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
GBM	glioblastoma
KM	Kaplan-Meier
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O^6-methylguanine-DNA methyltransferas
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	objective response rate
OS	overall survival
PD	progressive disease
PK	pharmacokinetic
PFS	progression-free survival
PR	partial response
PT	preferred term
RANO	Response Assessment in Neuro-Oncology
RT	radiotherapy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease

SOC	system Organ Class
SPD	sum of the products of the perpendicular diameter
TEAE	treatment-emergent adverse event
TMZ	temozolomide
unmethylated GBM	GBM with unmethylated MGMT promoter

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 and report results for BGB-290-104 protocol Version 2.0, dated July 23rd 2018: A Phase 1b/2 study to assess the safety, tolerability and efficacy of pamiparib in combination with radiation therapy (RT) and/or temozolomide (TMZ) in patients with first-line or recurrent/refractory glioblastoma (GBM). The focus of this SAP is for the planned primary, secondary efficacy and safety analyses specified in the study protocol.

2 STUDY OVERVIEW

This is an open-label, multicenter, multiple-dose, dose-escalation Phase 1b/2 study to determine the safety and pharmacokinetics (PK) of pamiparib in combination with radiation therapy and/or temozolomide with two initial arms (arms A and C) and a potential third arm (arm B). In arm A, pamiparib will be combined with RT in patients with first-line GBM with unmethylated MGMT promoter ('unmethylated GBM'). In arm B, depending on the safety of the arm A combination, pamiparib will be combined with both TMZ and RT in patients with first-line unmethylated GBM. In arm C, pamiparib will be combined with TMZ in patients with recurrent/refractory GBM with methylated or unmethylated MGMT promoter.

On completion of escalation cohorts, the study planned to enroll expansion cohorts for arm C and depending upon the emerging data, either arm A or arm B. Under protocol Version 2.0, dated July 23rd 2018, following completion of radiation treatment in Arms A and B , at the discretion of the investigator and after discussion with the medical monitor, patients may continue to receive pamiparib in combination with TMZ (maintenance).

Disease status will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria. Patients will undergo tumor assessments at screening and then every 8 weeks, or as clinically indicated.

3 STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVES

3.1.1. Phase 1b

Arm A (pamiparib + RT): Patients with first-line unmethylated GBM

- To assess safety and tolerability of pamiparib combined with RT
- To identify dose-limiting toxicities (DLTs) and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and length of treatment for pamiparib combined with RT
- To select the recommended Phase 2 schedule for pamiparib combined with RT

Arm B (pamiparib + RT + TMZ): Patients with first-line unmethylated GBM

- To assess safety and tolerability of pamiparib combined with RT and TMZ
- To identify DLTs and determine the MTD or MAD for TMZ when combined with RT and the length of pamiparib treatment in combination with RT as determined in arm A
- To select the recommended phase 2 dose (RP2D) for TMZ when combined with RT and the length of pamiparib treatment as determined in arm A

Arm C (pamiparib + TMZ): Patient with recurrent/refractory GBM

- To assess safety and tolerability of pamiparib combined with TMZ
- To identify DLTs and determine the MTD or MAD for TMZ combined with pamiparib
- To select the RP2D for TMZ combined with pamiparib

3.1.2 Phase 2

Arm A, Expansion (pamiparib + RT): Patients with first-line unmethylated GBM

- To make a preliminary assessment of efficacy of pamiparib combined with RT followed by maintenance treatment of pamiparib + TMZ for those patients continuing onto maintenance treatment

Arm C, Expansion (pamiparib + TMZ): Patients with recurrent/refractory unmethylated or methylated GBM

- To make a preliminary assessment of efficacy of pamiparib combined with TMZ

3.2 SECONDARY OBJECTIVES

Phase 1b, all Arms

- Characterize the PK of pamiparib in combination with RT and/or TMZ
- To make a preliminary assessment of pamiparib efficacy in combination with RT and/or TMZ

Phase 2, Arm A and C

- To further characterize the efficacy, safety and tolerability of pamiparib in combination with RT and/or TMZ
- To further characterize the PK of pamiparib in combination with RT and/or TMZ

4 STUDY ENDPOINTS

4.1 PRIMARY ENDPOINTS

Phase 1b, all Arms

- Incidence and nature of DLTs

- Incidence, nature, and severity of AEs, graded according to the NCI-CTCAE, v4.03
- Number of cycles (arm C and maintenance phase for arm A&B) and the dose intensity of each component of the treatment regimens, and changes in vital signs and clinical laboratory test results during and following study treatment

Phase 2, ArmA (pamiparib + RT)

- Modified disease control rate (mDCR) as assessed using the Response Assessment in Neuro-Oncology (RANO) criteria

Phase 2, Arm C (pamiparib + TMZ)

- Overall response rate (ORR) as assessed using RANO criteria

4.2 SECONDARY ENDPOINTS

Phase 1b, all Arms

- PK parameters of pamiparib: trough plasma concentration (C_{trough})
- Modified DCR (Arms A and B), DCR (Arm C), ORR and clinical benefit rate (CBR)
- Time-to-event endpoints: duration of response (DOR), progression-free survival (PFS) and overall survival (OS)

Phase 2, Arm A (pamiparib + RT)

- ORR and CBR as assessed using RANO
- Time-to-event endpoints: DOR, PFS and OS
- Incidence, nature, and severity of AEs, graded according to NCI-CTCAE, v4.03
- The dose intensity of each component of the treatment regimens, and changes in vital signs and clinical laboratory test results during and following study treatment
- PK parameters of pamiparib: C_{trough}

Phase 2, Arm C (pamiparib + TMZ)

- DCR and CBR as assessed using RANO criteria
- Time-to-event endpoints: DOR, PFS and OS
- Incidence, nature, and severity of AEs, graded according to NCI-CTCAE, v4.03
- Number of cycles and the dose intensity of each component of the treatment regimens, and changes in vital signs and clinical laboratory test results during and following study treatment
- PK parameters of pamiparib: C_{trough}

5 SAMPLE SIZE CONSIDERATIONS

Approximately 300 patients (60 in Phase 1b and 240 in Phase 2) were originally planned for enrollment. The actual sample size in Phase 1b depended on the number of Cohorts enrolled per arm and was 46 patients. The overall sample size was reduced during the study since the expansion cohorts were considered too large for this nonrandomized and nonregistrational study. The sample size in arm A expansion cohort is 40 and the sample size in arm C expansion cohort is 30. Overall the total number of patients enrolled in this study was 116.

Due to the reduction in sample size of the arm C expansion cohort, the analysis will not separate patients by MGMT status.

In Phase 2, the original sample size calculation was carried out using modified DCR in Arms A and B and ORR in each expansion cohort of arm C.

1) Assuming modified DCR of 60% in Arms A and B vs. 40% in historical control, the study is powered at ~82% to show 20% difference in modified DCR using a one-sided alpha of 0.025 when n = 60 per expansion cohort. Due to the reduction in actual sample size to 40 patients, assuming an observed modified DCR of 60%, the lower bound of the 80% exact confidence interval (CI) for the estimated modified DCR will exclude values less than 48%. The minimum observed modified DCR that has an 80% exact CI excluding 40% will be 53% (21 out of 40).
2) Assuming ORR of 25% in arm C vs. 10% in historical control, the study is powered at ~85% to show an 15% difference in ORR using a one-sided alpha of 0.025 when n=60 per expansion cohort. Due to the reduction in actual sample size to 30 patients, assuming an observed ORR of 25%, the lower bound of the 80% exact CI for the estimated ORR will exclude values less than 16%. The minimum observed ORR that has an 80% exact CI excluding 10% will be 20% (6 out of 30).

6 STATISTICAL METHODS

6.1 ANALYSIS POPULATIONS

Safety Analysis Set: includes all patients who received any dose of any of the study treatments (pamiparib, RT and/or TMZ). The Safety Analysis Set will be used for efficacy and safety analyses.

Efficacy Analysis Set: includes all patients in the Safety Analysis Set who:

Arms A & B: had a tumor assessment at baseline and at End of Treatment unless discontinued treatment or study early due to disease progression or death prior to tumor assessment.

Arm C: had measurable disease at baseline and at least one postbaseline tumor assessment unless discontinued treatment or study early due to disease progression or death prior to tumor assessment.

DLT-Evaluable Analysis Set: includes patients from escalation cohorts only in the Safety Analysis Set who received ≥ 42 Gy of RT (Arms A and B) and ≥ 70% of scheduled pamiparib (Arms A, B and C) and TMZ (Arms B and C) during the DLT assessment window. All patients who had a DLT event will be considered DLT-evaluable regardless of study treatment intensity.

PK Analysis Set: includes all patients for whom valid pamiparib PK parameters can be estimated.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the first dose date of study drug. First dose date of study drug is defined as the earliest date of the first dose of any study drug. For maintenance phase, C1D1 is the first dose date. For assessments conducted on or after the first dose date, study day will be calculated as (assessment date – first dose date of study drug + 1). For assessments conducted before the first dose date, study day is calculated as (assessment date – first dose date 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 1.

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

Treatment Duration:

Arm A&B regular treatment period (with RT) is defined as date of the last non-zero dose of latest treatment – first dose date of earliest treatment +1; treatment duration

Arm A&B maintenance period is defined as last non-zero dose of latest treatment in maintenance phase – date of C1D1 of maintenance phase +1

Arm C is defined as date of last non-zero dose of latest treatment – first dose date of earliest treatment +1.

RANO assessments:

ORR (objective response rate) is defined as proportion of patients with best overall response of CR or PR per RANO criteria (confirmed by a subsequent tumor assessment at least four weeks apart). Best overall response will be assessed from the start of study treatment until data cut-off date, disease progression or start of new anti-cancer therapy. Patients without postbaseline tumor assessment are considered non-responders.

Modified DCR (disease control rate) is defined as the proportion of patients with CR, PR or SD per RANO criteria as the response assessment at the end-of-treatment (EOT) visit, as

scheduled per protocol. Patients with no EOT tumor assessment, as scheduled per protocol (due to any reason), will be considered non-responders for modified DCR.

DCR (disease control rate) is defined as the proportion of patients with best overall response of CR, PR or SD per RANO criteria. CR or PR will be confirmed by a subsequent tumor assessment at least four weeks apart.

CBR (clinical benefit rate) is defined as the proportion of patients with best overall response of CR, PR or SD ≥ 24 weeks per RANO criteria. CR or PR will be confirmed by a subsequent tumor assessment at least four weeks apart.

BOR (best of response) is defined as the best response recorded from the start of study treatment until data cutoff, or start of new anti-cancer therapy. Computation of BOR will consider timepoints prior to PD when determining BOR.

Time to event data

OS (overall survival) is defined as the time from the first dose date to date of death for any cause. Patients that are still alive at the time of analysis will be censored at the last contact date that is known to be alive.

PFS (progression free survival) is defined as the time from the first dose date to disease progression per RANO criteria or death, whichever occurs first. Censoring rules for PFS are described in Table 1 in section 6.4.2.

DOR (duration of response) is defined as the time from the date of the earliest documented response to disease progression or death for any cause whichever occurs earlier.

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 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days / 30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (first dose date – date of birth + 1)/3 65.25
- 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'.
- 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 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), unless otherwise specified.
- 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 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.

6.2.4 Handling of Treatment Cycles

In arm C, patients will be treated in a 28 days cycle. The schedule of each cycle will not change for dose delays or dose holds.

During maintenance treatment in Arms A and B, patients will be treated in a 28 days cycle. The schedule of each cycle will not change for dose delays or dose holds.

6.2.5 Adjustment for Covariates

No covariates will be adjusted in primary analyses.

6.2.6 Data Integrity

Before the 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 number (percentage) of subjects treated, discontinued from study treatment, entered efficacy and survival follow-up phase, discontinued from study and duration of follow-up will be summarized. The primary reason for treatment and study discontinuation will be summarized according to the categories in 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 presented in a listing by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using descriptive statistics in the Safety Analysis Set.

Continuous variables include:

- Age (years)
- Time (weeks) from initial diagnosis of glioblastoma to first dose date
- Time (weeks) from initial surgical resection

Categorical variables include:

- Age group (< 65, ≥65 years)
- Gender (Male, Female)
- Race (Asian, Black or African American, White, others)
- ECOG performance status (0, 1)
- Surgical status for initial diagnosis of glioblastoma (biopsy, partial resection, complete resection and no prior surgery)
- Baseline corticosteroids use (yes, no)
- Relapse status (arm C only)
- MGMT promoter status (arm C only)
- Prior use of temozolomide (arm C only)
- WHO grade at initial diagnosis (arm C only)

6.3.4 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 by phase in the Safety Analysis Set. Prior medications are defined as medications that started 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 anti-cancer therapy. A listing of prior and concomitant medications will be provided.

6.3.5 Prior GBM Related Therapy (arm C only)

The number (percentage) of prior GBM related anti-cancer systemic therapies, surgical history and radiation therapy will be summarized in the Safety Analysis Set.

6.3.6 Medical History

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

6.4 EFFICACY ANALYSIS

The primary efficacy analysis will be conducted when mature response data have been observed, which will be determined by the Sponsor.

An independent read of the tumor scans by Independent Review Committee (IRC) was planned at the beginning stage of the study. Following sample size reduction and due to the nonrandomized and nonregistrational nature of the study, the decision was made that independent reads would not be requested and investigator-evaluated assessments would be used to calculate ORR, DCR, CBR, DOR and PFS.

6.4.1 Primary Efficacy Endpoints

Efficacy analysis will be performed on all patients for all arms. For Arm A and Arm C, phase 1b and phase 2 are presented in different table columns.

Arm A and Arm B

Modified Disease Control Rate is the primary efficacy endpoint in Arms A and B. It is defined as the proportion of patients with CR, PR or SD per RANO criteria as the response assessment at the end-of-treatment (EOT) visit, as scheduled per protocol. Patients with no EOT tumor assessment, as scheduled per protocol (due to any reason), will be considered non-responders for modified DCR. Modified DCR of Pamiparib combination therapy is assumed as 60% in the study population. The historical rate in a similar population is estimated as 40% (Rivera et al., 2010). No formal hypothesis testing will be performed. Two-sided binomial exact 80% and 95% CI of modified DCR will be constructed to assess the precision of the rate estimate.

Arm C

Objective Response Rate (ORR) is the primary efficacy endpoint in arm C. The analysis will be performed for the efficacy analysis set. It is defined as proportion of patients with best overall response of CR or PR per RANO criteria (confirmed by a subsequent tumor assessment at least four weeks apart). Best overall response will be assessed from the start of study treatment until data cut-off date, disease progression or start of new anti-cancer therapy. Patients without postbaseline tumor assessment is considered nonresponders. ORR of Pamiparib combination therapy is assumed as 25% in the study population. The historical rate in a similar population is

estimated as 10% (Chen et al, 2013). Two-sided binomial exact 80% and 95% CI of ORR will be constructed to assess the precision of the rate estimate.

In addition, the number (%) of the best overall response categories (CR, PR, SD, PD) will be presented.

6.4.2 Secondary Efficacy Endpoints

Disease Control Rate (DCR – for arm C)

DCR is defined as the proportion of patients with best overall response of CR, PR or SD per RANO criteria. CR or PR will be confirmed by a subsequent tumor assessment at least four weeks apart. DCR will be performed in similar fashion as described in primary endpoint modified DCR on Efficacy Analysis Set.

Objective Response Rate (ORR – for arm A&B)

ORR for arm A&B will be performed for Efficacy Analysis Set in similar fashion as in primary endpoint for arm C.

Progression-Free Survival (PFS)

PFS is defined as the time from the first dose date to disease progression per RANO criteria or death, whichever occurs first. PFS analysis will be performed for all arms using Safety Analysis Set.

PFS censoring rule will follow FDA *Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer drugs and Biologics* (2007). The censoring rules are described in Table 1. If a patient meets the criteria for more than 1 censoring rule, PFS will be censored at the earliest censoring date.

Table 1 Censoring Rules for Analysis of Progression-Free Survival

Censoring Categories	Date of Progression or Censoring	Outcome
Progression documented on scheduled visit or between scheduled visits	Date of first PD assessment	Progressed
Death before first tumor assessment	Date of death	Progressed
Death between scheduled adequate assessment visits	Date of death	Progressed
No baseline or postbaseline tumor assessments	Date of the first dose	Censored
No PD or death at the time of data cut-off or withdrawal from study	Date of last adequate radiologic tumor assessment prior to or on date of data cut-off or withdrawal from study	Censored

New anticancer treatment started	Date of last adequate radiologic tumor assessment prior to or on date of new anticancer treatment	Censored
Death or PD immediately after two or more missed visits	Date of last adequate radiologic tumor assessment before missed tumor assessments	Censored

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.

Duration of Response (DOR)

DOR is defined as the time from the date of the earliest documented response (confirmed or unconfirmed) of CR or PR to disease progression or death for any cause, whichever occurs earlier. Only responders will be included in the DOR analysis. Censoring rule for DOR will follow PFS censoring rule.

Overall Survival (OS)

OS is defined as the time from the date of first study treatment to death of any cause. Patients who have not died by the analysis cutoff date will be censored at the last date known to be alive or the data cutoff date, whichever is earlier. OS will be performed for Safety Analysis Set.

Time-to-event variables PFS, OS and DOR will be estimated using the Kaplan-Meier (KM) method. KM estimates of PFS, DOR and OS will be plotted over time. Median PFS, DOR and OS, if possible to estimate, in each arm will be presented, along with their 2-sided 95% CIs using Brookmeyer and Crowley method (Brookmeyer & Crowley, 1982). The PFS-6m, PFS-12m, OS-6m, and OS-12m, defined as the proportion of patients in the Safety Analysis Set who remain alive and progression-free at 6 months and 12 months (or alive at 6 month and 12 months for OS), will be estimated using KM method along with the corresponding 95% confidence interval constructed using Greenwood's formula (Greenwood, 1926).

6.4.3 Subgroup Analyses

Modified DCR (Arms A & B combined) and ORR (arm C) will be summarized for following subgroups:

- Age (< 65, ≥ 65)
- Gender (Female and Male)
- Race (white, nonwhite)
- ECOG performance status (0, 1)
- Prior surgery status (biopsy only, partial resection, complete resection)
- Baseline corticosteroid use (yes, no)
- Methylation status (arm C only)

- Relapse status for arm C ORR only (first relapse, second relapse)

Forest plot will be provided for these subgroups as well. These planned subgroup analyses may not be explored if sufficient number of samples cannot be achieved for certain subgroups. The subgroup variables and the cutoff values are patient to change if warranted to better represent the data.

6.5 SAFETY ANALYSES

All safety analyses will be performed by dose cohorts (Phase 1b and Phase 2 will be presented as different table columns) and arms (A, B and C). 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, and ECGs findings will also be used in determining the safety. Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables) will be used to analyze all safety data in the safety population.

6.5.1 Extent of Exposure

Descriptive summaries will be provided by cohort and each arms for following variables:

- Number of cycles received (in arm C and in Arms A and B for maintenance patients)
- Treatment duration (days) for all arms (see section 6.2.1 for definitions)
- Number of patients require dose interruptions and reductions
- Total dose received per patient (mg for pamiparib and TMZ, and Gy for RT)
- Dose intensity (mg/day for pamiparib and TMZ) and relative dose intensity. Dose intensity per patient is defined as sum of actual dose received divided by planned duration of treatment. Relative dose intensity is defined as total actual dose received divided by total planned dose. Total planned dose is the total dose that would be delivered, if there were no modification to dose or schedule.

Patients with dose reductions and interruptions and the reasons for reductions and interruptions will be listed.

6.5.2 Dose Limiting Toxicity

Dose-limiting toxicity in the DLT evaluation period will be assessed to determine the dose and schedule in phase 2. DLT events from the adverse event eCRF will be summarized descriptively for each dose cohort and arm in phase 1b in the DLT evaluable population.

6.5.3 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 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 first dose of study treatment or was worsening in severity from baseline (pretreatment) up to 30 days following permanent study treatment discontinuation or initiation of new anti-cancer therapy, whichever occurs first. All AEs, treatment emergent or otherwise, will be presented in patient data listings. TEAEs will be summarized and presented for all cohorts and all arms.

An overview table, including the number and percentage of patients with any TEAEs, any treatment-related TEAEs, treatment-emergent serious adverse events (SAEs), TEAEs with grade 3 or above, treatment-related SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related AEs include those events considered by the investigator to be unlikely, possibly or probably or definitely related to study drug or with missing assessment of the causal relationship. The overview table will be completed for each study Arm.

The following TEAEs will also be tabulated in summary tables for all arms and cohorts:

- TEAE
- SAE
- TEAEs with grade 3 or above
- Treatment-related TEAEs
- Treatment-related SAEs
- TEAEs that led to death
- TEAEs leads to treatment discontinuation
- TEAEs leads to dose reduction or dose interruption of either Pamiparib or RT or TMZ

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. TEAEs with grade 3 or above will also be summarized by PT in descending order.

In addition, the following listings will be provided:

- Listing of all AEs,
- Listing of all SAEs
- Treatment-related AEs
- Grade 3 or above AEs
- AEs leading to death
- AEs leading to treatment discontinuation

6.5.4 Laboratory Values

Clinical laboratory values will be evaluated for selected parameters described in table 2.

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	
Creatinine	
Chloride	
Phosphate	
Glucose	
Lactate dehydrogenase	
Total Protein	
Potassium	
Sodium	

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferases, WBC = white blood cell

For all quantitative parameters listed in Table 2, 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 summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables). Qualitative parameters listed in Table 2 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.

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

6.5.5 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature, height 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)

Single 12-lead ECGs will be collected at screening and end of treatment. Additional ECGs will be performed if clinically indicated. The percentage of patients with abnormal and clinical significant ECGs at EOT will be presented.

6.5.7 Eastern Cooperative Oncology Group (ECOG)

ECOG scores and change from baseline will be summarized by visit using Safety Analysis Set.

6.6 PHARMACOKINETIC ANALYSES

6.6.1 Plasma Concentrations

Pharmacokinetic samples will be collected from patients in all cohorts at the following time points: predose (within 30 min prior to dose) and 2 hours (± 30 min) post-dose on both Day 1 and Day 15 (collection takes place in Cycle 1 for arm C). If pamiparib treatment is administered only for a 2-week (14-day) time period, PK samples will be collected on Day 1 and Day 14 instead. The time of study drug administration on the day prior to Day 15 (Day 14 for patients receiving only 2 weeks of pamiparib) must be recorded on the eCRF. Details concerning collection, handling, and processing of the PK plasma samples will be provided in the laboratory manual.

Plasma pamiparib concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard noncompartmental and/or compartmental methods. 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 time point by dose level. 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.

7 INTERIM ANALYSIS

No interim analysis is planned.

8 CHANGES IN THE PROTOCOL PLANNED ANALYSIS

1. Sample size reduction: The overall sample size was reduced during the study since the expansion cohorts were considered too large for this non-randomized and non-registrational study.
2. All arm B expansion cohort related analysis and language are removed since it was decided not to enroll expansion cohort for arm B

3. Primary analysis will be performed on efficacy analysis set, not safety analysis set. No sensitivity analysis will be performed.
4. Exploratory objectives and endpoints in the protocol will not be explored in this SAP

9 REFERENCES

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10 APPENDIX

Appendix 1. Imputation of Missing/Partially Missing Dates

Missing data will not be imputed unless otherwise specified. The imputation rule for the safety analyses will be used to address the issues with partial dates. When the start date or end date of an adverse event is partially missing, the date will be imputed to determine whether the adverse event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

Adverse Events

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

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

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

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

- If both month and day are missing, then set to December 31.
- If only day is missing, then set to last day of the month.
- If end date is completely missing, do not impute.

Prior/Concomitant Medications, Disease and Medical History, Prior Therapy

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

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

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

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

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 the last date of patient known to be alive + 1, whichever is later.
- If only day is missing: If last known alive date is in same month as death date, then death date= last known alive date+1;If death month is after last known alive date, then use first day of the month as death date.

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.