CLINICAL STUDY PROTOCOL

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**
Protocol Number:	**BGB-290-104**
Investigational Product	**Pamiparib (BGB-290)**
Original Protocol (Version 1.0):	**17 February 2017**
Protocol Version 2.0	**23 July 2018 (Final)**
IND No.:	**135006**
EudraCT No.:	**2017-001554-33**
Study Phase:	**1b/2**
Sponsor:	**BeiGene USA, Inc.** **2115 Linwood Avenue** **Fort Lee, NJ 07024** **United States**
Sponsor Medical Monitor:	[redacted]

SIGNATURES

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

PROTOCOL NO: BGB-290-104

[redacted]

27-July-2018

Date

Sponsor Medical Monitor

SYNOPSIS

Name of Sponsor/Company:	**BeiGene USA, Inc.**
Name of Finished Product:	**Pamiparib (BGB-290)**
Name of Active Ingredient:	**Pamiparib (BGB-290)**
Title of Study:	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
Protocol No:	BGB-290-104
Number of Patients:	Approximately 300 patients (60 in Phase 1b and 240 in Phase 2) may be enrolled. The actual sample size in Phase 1b will depend on the number of cohorts enrolled per arm.
Study Centers:	Approximately 15 to 40 centers in the United States, Europe, and/or Australia
Study Phase:	Phase 1b/2
Treatment Duration:	Arm A (dose escalation and dose expansion): Patients will be treated with pamiparib (also known as BGB-290) + radiation therapy (RT) for a maximum of 6 to 7 weeks. Arm B (dose escalation and dose expansion): Patients will be treated with pamiparib + RT + temozolomide (TMZ) for a maximum of 6 to 7 weeks. In Arms A and B of the dose-escalation phase, after RT is completed, at the discretion of the investigator and after discussion with the medical monitor, patients may continue to receive pamiparib in combination with TMZ (maintenance). In the Arm A expansion phase of the study, continuation of treatment (with pamiparib in combination with TMZ) will be at the discretion of the Investigator after discussion with the Medical Monitor. In the Arm B expansion phase of the study, maintenance treatment will be mandatory for all patients. Arm C (dose escalation and dose expansion): Patients will be treated with pamiparib + TMZ. In all 3 arms, patients will continue receiving study drug(s) until progressive disease (PD), unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor.

Objectives:

Primary:

Phase 1b

Arm A (pamiparib + RT): Patients with first-line glioblastoma multiforme (GBM) with unmethylated *MGMT* promoter (unmethylated GBM)

- To assess safety and tolerability of pamiparib combined with RT
- To identify dose-limiting toxicity (ies) (DLTs) and determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) 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 MTD/MAD of pamiparib determined in Arm A
- To select the recommended phase 2 dose (RP2D) for TMZ when combined with RT and the MTD/MAD for pamiparib determined in Arm A

Arm C (pamiparib + TMZ): Patients 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

Phase 2

Arm A, Expansion 1 (pamiparib + RT): Patients with first-line unmethylated GBM

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

Arm B, Expansion 1 (pamiparib + RT + TMZ): Patients with first-line unmethylated GBM

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

Arm C, Expansion 1 (pamiparib + TMZ): Patients with recurrent/refractory unmethylated GBM

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

Arm C, Expansion 2 (pamiparib + TMZ): Patients with recurrent/refractory methylated GBM

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

Secondary:

Phase 1b, all Arms

- To characterize the pharmacokinetics (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, all Arms

- 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

Exploratory:

[redacted]

Study Design:

This is an open-label, multi-center, multiple-dose, dose-escalation Phase 1b/2 study to determine the safety, PK, and pharmacodynamics of pamiparib in combination with RT and/or TMZ 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.

Dose Escalation Phase

The dose escalation phase consists of the following:

Arm A: Pamiparib (60 mg BID) administered continuously at increasing exposures of 2, 4, and 6 weeks in combination with RT administered for 6 to 7 weeks.

Arm B: Depending on the safety of the Arm A combination, the following combination may be explored: pamiparib (at the exposure determined as safe in Arm A) in combination with RT administered for 6 to 7 weeks and increasing doses of TMZ.

In both Arms A and B, after RT is completed, patients will receive no further RT.

Maintenance Treatment for Arms A and B: Following completion of RT, at the discretion of the investigator and after discussion with the medical monitor, patients in Arm A escalation and expansion and Arm B escalation phases of the study may continue to receive pamiparib in combination with TMZ.

In the Arm B expansion phase of the study, maintenance treatment will be mandatory for all patients.

Dosing for this maintenance regimen should begin after the 4-week rest period (+ 7 days) to allow for recovery from RT treatment (as per Appendix 1 Table 4).

Arm C: Pamiparib (60 mg BID, administered continuously) in combination with increasing doses of TMZ administered on Days 1 to 21 of each 28-day cycle.

Approximately 60 patients may be enrolled during the dose escalation phase. The actual sample size in this phase will depend on the number of dose escalation cohorts enrolled per arm.

Dose Expansion Phase

Once the safety, tolerability, PK, pharmacodynamic, and preliminary antitumor activity have been reviewed for the dose escalation cohorts of each of the arms, up to approximately 60 patients may be enrolled in expansion cohorts for each of the 3 arms at a dose level below or equal to the MTD or MAD for that arm. In Arm C, 2 expansion cohorts may be opened, one for unmethylated GBM and one for

methylated GBM (Protocol Section 4.3). Therefore, a total of approximately 240 patients may be enrolled in the dose expansion phase.

Adverse events (AEs) during and after the treatment period with study drug(s) will be followed and documented as outlined in Protocol Section 8.4 and Section 10. AEs will be graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4.03. To determine the PK properties of pamiparib, blood samples will be obtained coinciding with specific PK time points as outlined in Protocol Section 8.5 and Protocol Appendix 1.

Disease status will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria (Appendix 2). Patients will undergo tumor assessments at Screening and then every 8 weeks, or as clinically indicated.

Patients in Arms A and B who have completed all study treatments per protocol and do not continue on pamiparib in combination with TMZ (maintenance) will have their end-of-treatment (EOT) visit at the end of the Rest Phase, 28 days after RT was completed, unless they do not complete the full study treatment; in such a case they should have the EOT visit within 7 days of stopping all study treatment. All other patients who have discontinued all study treatments should return to the clinic for an EOT visit within 7 days of stopping all treatment. After the EOT visit, all patients should have regular follow-up for safety, efficacy, and survival as outlined in Protocol Section 6.6.

Patients will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) approximately every 12 weeks as per Protocol Appendix 1.

Study Population:

Inclusion criteria

Patients must meet all of the following criteria to be eligible for the study:

For all patients

1. Signed Informed Consent Form (ICF)
2. Age ≥18 years
3. Histopathologically confirmed glioblastoma (World Health Organization [WHO] Grade IV) (Louis et al, 2016)
    - Tumor must have a supratentorial component.
4. [redacted]
5. Ability to undergo serial magnetic resonance imaging (MRI) scans (computerized tomography [CT] cannot substitute for MRI)
6. Brain MRI scan ≤ 14 days prior to Day 1
    - Patients requiring glucocorticoids must be on a daily dose equivalent of dexamethasone 4 mg twice daily or less that has been stable for ≥ 7 days prior to the MRI.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 (Protocol Appendix 3)
8. Ability to swallow whole capsules

9. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 2 weeks prior to Day 1):
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Hemoglobin ≥ 9 g/dL ≥ 14 days after growth factor support or transfusion if appropriate
   - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 50 mL/min (calculated using the institutional standard method)
   - Total serum bilirubin ≤ 1.5 x ULN (≤ 4 x ULN, if Gilbert's syndrome)
   - Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 x ULN
   - Albumin ≥ 3 g/dL
   - International Normalized Ratio (INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
10. Female patients of childbearing potential and female partners of male study patients must agree to practice highly effective methods of birth control (Protocol Appendix 4) for the duration of the study and for ≥ 6 months after the last study treatment. In addition, non-sterile male patients must agree to practice highly effective methods of birth control (Protocol Appendix 4) and avoid sperm donation for the duration of the study and for ≥ 6 months after the last dose of study drug
11. Willingness and ability to comply with all protocol-specified requirements

→For patients in Arms A and B (NOT applicable to Arm C)

12. No previous treatment except surgery (ie, no previous RT, local chemotherapy, or systemic therapy for lower grade central nervous system tumors)
13. Ability to initiate RT ≤ 49 days after surgery, but ≥ 14 days after a biopsy or ≥ 28 days after an open biopsy or a craniotomy with adequate wound healing
14. Documentation of unmethylated *MGMT* promoter status
    - In escalation cohorts, it is preferable to determine *MGMT* status by quantitative methylation-specific polymerase chain reaction (MS-PCR). Other acceptable platforms include pyrosequencing methodologies and methylation sensitive high-resolution melting (MS-HRM) assays with comparable sensitivity, applied to archival or fresh tumor tissue. Sponsor must be notified prior to utilizing alternate assays or if data from acceptable alternate platforms are available.
    - In expansion cohorts, archival or fresh tumor tissue must be submitted for central analysis of *MGMT* status.

→For patients in Arm C Escalation (*NOT applicable to Arms A and B*)

15. Documentation of *MGMT* promoter status
    - It is preferable to determine *MGMT* status by MS-PCR. Other acceptable platforms include pyrosequencing methodologies and MS-HRM assays with comparable sensitivity, applied to archival or fresh tumor tissue. Sponsor must be notified prior to utilizing alternate assays or if data from acceptable alternate platforms are available.

16. No prior systemic chemotherapy, other than TMZ, for glioblastoma (including investigational cytotoxic chemotherapy), and no prior anti-angiogenic therapy
    - Prior use of Optune device is allowed with a minimum of 1 week since last Tumor Treating Fields application
17. Histologically confirmed *secondary* glioblastoma will be allowed during the dose escalation phase only
18. Disease that is evaluable or measurable as defined by RANO criteria (Protocol Appendix 2)

→For patients in Arm C Expansion

19. Histologically confirmed *de novo* (primary) glioblastoma with unequivocal first progressive disease (PD) after RT with concurrent/adjuvant TMZ chemotherapy as defined by one or more of the following:
    - PD ≥ 3 months after the end of radiotherapy
    - PD that is clearly outside the radiation field
    - PD that has been unequivocally proven by surgery/biopsy
20. Disease that is measurable as defined by RANO criteria (Protocol Appendix 2)
    - Patients with recurrent disease must have at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices
21. Documentation of *MGMT* promoter status
    - Tumor tissue (archival or fresh) must be submitted for central analysis of *MGMT* status
    - Patients will be enrolled into 1 of 2 expansion cohorts based on *MGMT* methylation status

Exclusion criteria

Patients will be excluded from the study for any of the following reasons:

For all patients

1. Chemotherapy, biologic therapy, immunotherapy, or investigational agent ≤ 21 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1
2. Unresolved acute effects of any prior therapy of Grade ≥ 2, except for AEs not constituting a safety risk by investigator judgement
3. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
    - Placement of vascular access device is not considered major surgery
4. Other diagnosis of malignancy
    - Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, adequately treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy

diagnosed >2 years ago with no current evidence of disease and no therapy ≤ 2 years prior to Day 1

5. Active infection requiring systemic treatment
6. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection:
    - Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL or patients with active hepatitis C virus (HCV) should be excluded. Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA ≤ 500 IU/mL), and cured patients with hepatitis C can be enrolled.
7. Any of the following cardiovascular criteria:
    - Current evidence of cardiac ischemia
    - Current symptomatic pulmonary embolism
    - Acute myocardial infarction ≤ 6 months prior to Day 1
    - Heart failure of New York Heart Association Classification III or IV (see Protocol Appendix 5) ≤ 6 months prior to Day 1
    - Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Day 1
    - Cerebral vascular accident (CVA) or transient ischemic attack (TIA) ≤ 6 months prior to Day 1
8. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease, or previous gastric resection or lap-band surgery
    - Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed (assuming no drug interaction potential)
9. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months prior to Day 1
10. Anticoagulation with heparin, warfarin, or other anticoagulants other than the following:
    - Low-dose aspirin and/or non-steroidal anti-inflammatory agents are allowed
    - Use of thrombolytics to establish patency of indwelling venous catheters is allowed
    - Prophylactic anticoagulation for venous access devices is allowed as long as INR is ≤ 1.5 and aPTT ≤ 1.5 × institutional ULN
    - Low molecular weight heparin for treatment of thromboembolic events
11. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1 or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers including known enzyme inducing anti-epileptic drugs (Protocol Appendix 6)
12. Pregnancy or nursing
    - Females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1.
13. Significant intercurrent illness that may result in the patient's death prior to death from glioblastoma
14. Known history of intolerance to the excipients of the pamiparib capsule

→For patients in Arm B and C *(NOT applicable to Arm A)*

15. Known hypersensitivity to any temozolomide component or to dacarbazine (DTIC)
16. Have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

Study Drug and Treatment:	Pamiparib: **Arm A, Arm B,** and **Arm C:** 60 mg will be administered orally (PO) twice daily (BID), once in the morning and once in the evening. The time difference between 2 consecutive doses should be approximately 8 to 12 hours. Radiation therapy: **Arm A** and **Arm B:** RT will be administered once daily (QD) × 5 days/week for 6 to 7 weeks with 1.8 or 2 Gy/fraction for a total target dose of between 58 Gy and 64 Gy. Temozolomide: **Arm B** and **Arm C:** flat-dosing will be used for TMZ. For Arm C, the first dose level of 40 mg PO QD corresponds to 23 mg/m^2 assuming an average body surface area of 1.73 m^2. Subsequent dose levels of 80 mg and 120 mg, corresponding to 46 mg/m^2 and 69 mg/m^2, respectively, will be administered PO QD. For Arm B, the first dose level of TMZ will be lower than or equal to a dose that has been determined to be safe and tolerable in Arm C.

Dose Modifications:

RT should only be modified for AEs determined to be solely or mostly related to RT as typically done per standard of care.

Dosing of pamiparib and TMZ can be interrupted for approximately 28 days for medical events that are not associated with toxicity related to these study drugs or disease progression.

Criteria for treatment modifications and suggested guidelines for the management of toxicities related to pamiparib and/or TMZ are summarized below.

Dose level	Temozolomide (TMZ)[1]	
	Flat dosing QD	*Dose equivalent*
-1	20 mg	*12 mg/m^2*
1	40 mg	*23 mg/m^2*
2	80 mg	*46 mg/m^2*
3	120 mg	*69 mg/m^2*
4	TBD	-

Dose level	Pamiparib[2]	
	BID	*QD*
-2	20 mg	*40 mg*
-1	40 mg	*80 mg*
1	60 mg	*120 mg*
	-	-
	-	-

Note: TMZ will be dose-reduced first for a maximum of 2 dose reductions. After discussions with the medical monitor, pamiparib may be dose-reduced next for a maximum of 2 dose reductions. Depending on the toxicity that is triggering a second TMZ dose reduction, the possibility of a concurrent pamiparib dose reduction should be discussed with the medical monitor. Once a dose of pamiparib or TMZ has been reduced, re-escalation is not allowed. A patient must discontinue

treatment with pamiparib and TMZ, if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity.

BID = twice daily; QD = once daily; TBD = to be determined

[1] Flat dosing of TMZ is used in this study. Dose equivalent information is provided for reference only and assumes an average body surface area of 1.73 m^2. The starting dose for Arm C is dose level 1. For Arm B, the first dose level of TMZ will be lower than or equal to a dose that has been determined to be safe and tolerable in Arm C.

[2] The dose for pamiparib used in this study is 60 mg BID. A QD schedule may be explored as outlined in Protocol Section 4.2.1.

The hold and discontinue guidelines for pamiparib (without TMZ) also apply in Arm A. After a toxicity has adequately resolved, the decision in Arm A of resuming pamiparib treatment at the same dose level versus dose-reducing pamiparib should be made in discussion with the Medial Monitor.

Concomitant Therapy and Clinical Practice:

Permitted Medications

All treatments and supportive care, including glucocorticoids, antiemetic therapy, hematopoietic growth factors and/or red blood cell/platelet transfusions, that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the local standards of medical care. All concomitant medications taken during the study will be recorded on the case report form (CRF) including all prescription and over-the-counter (OTC) drugs, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of that change in drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last day of study treatment should be recorded.

Prohibited Concomitant Therapy

Patients are not allowed to receive other anticancer therapy, including surgery, RT (other than protocol-specified), and cytotoxic, biologic, or hormone therapy. Hormone replacement therapy is allowed.

Therapeutic anticoagulation with heparin, warfarin, or other anticoagulants is not allowed, with the exception of low molecular weight heparin for treatment of patients with thromboembolic events.

Low-dose aspirin, non-steroidal anti-inflammatory agents, and thrombolytics to establish patency of indwelling venous catheters are allowed, as is prophylactic anticoagulation for venous access devices as long as INR is ≤1.5 and aPTT ≤1.5 × institutional ULN (Protocol Section 5.1).

Concomitant Use of CYP Inhibiting Drugs

The primary metabolic pathway for pamiparib involves the CYP3A isoform. The concurrent administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. In addition, pamiparib is an inhibitor of CYP2C9; careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Criteria for Evaluation:

Efficacy:

Tumor assessments will include all known or suspected disease sites. MRIs will be performed at screening (within 14 days of Day 1) and every 8 weeks (±7 days), unless otherwise specified in Appendix 1. Non-contrast cranial MRI may only be used to document disease in those patients who are allergic to contrast. Tumor assessments should be repeated at the end of treatment visit if more than 4 weeks have passed since the last evaluation. The same imaging technique used at screening should be

used throughout the study.

Anti-tumor activity will be assessed through radiologic tumor assessments conducted at screening, during treatment as specified in the Schedule of Activity, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks).

Assessment of response will be made using the RANO criteria (Protocol Appendix 2). Responses should be confirmed with 2 assessments at least 4 weeks apart. Efficacy evaluations using the RANO criteria involve post-contrast MRI findings, non-contrast T1 and T2 FLAIR images, use of corticosteroid dose, and clinical status per RANO (Ellingson et al 2015).

Following initial evidence of radiographic progressions and due to the potential for pseudo-progression patients may, at the discretion of the investigator, remain on treatment until further imaging is performed at 4 to 8 weeks (at the discretion of the investigator) after the initial determination of potential progression.

A central independent radiology facility (IRF) may evaluate imaging studies and supportive clinical data in a central and independent fashion. The IRF will comprise board-certified radiologists who will identify baseline lesions and assign post-baseline time point responses.

Safety:
Safety will be monitored throughout the study. Safety assessments include AE monitoring and reporting, physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory tests.

Endpoints:

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 only) 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, Arm A (pamiparib + RT) and Arm B (pamiparib + RT + TMZ)

- Modified disease control rate (DCR) as assessed using the RANO criteria (Appendix 2)

Phase 2, Arm C (pamiparib + TMZ)

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

Secondary Endpoints

Phase 1b, all Arms

- PK parameter for pamiparib: 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) and Arm B (pamiparib + RT + TMZ)

- ORR 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
- 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 parameter for 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 parameter for pamiparib: C_{trough}

Exploratory Endpoints

[redacted]

Statistical Methods:

Hypothesis testing will be performed in Phase 2. In addition, descriptive statistics will be used in describing the antitumor activity and tolerability of the combination regimens in each Phase. Confidence intervals will be constructed to describe the precision of the point estimates of interest (eg, ORR).

Tumor assessments by investigators according to RANO will be used to calculate ORR, modified DCR (Arms A and B), DCR (Arm C), PFS, DOR, and CBR, as well as time-point estimate PFS-6m. OS and OS at 6 months and 12 months (OS-6m and OS-12m), will be summarized in the efficacy analysis. An optional independent read of the MRI scans may be performed and will be analyzed in the same fashion.

Populations:

- The Safety Analysis Set includes all patients who received any study treatment (pamiparib, RT, and/or TMZ). The Safety Analysis Set will be used for all efficacy and safety analyses.
- The Efficacy-evaluable Analysis Set includes patients in the Safety Analysis Set who had baseline and at least one post-baseline tumor assessment, unless discontinued treatment or study early due to clinical progression or death prior to tumor assessment.
- The DLT-evaluable Analysis Set includes patients 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 with sufficient safety assessments. All patients who had a DLT event will be considered DLT-evaluable regardless of study treatment intensity.
- The PK Analysis Set includes all patients for whom valid pamiparib PK parameters can be estimated.

Primary Efficacy Analysis:

Phase 1b

As described in the protocol objectives, the trial is designed to establish the safety and tolerability of pamiparib in combination with RT and/or TMZ. Evidence of any antitumor activity will be documented and summarized for the Safety Analysis Set as secondary endpoints of the trial.

Phase 2 (Arms A and B)

Modified DCR is the primary efficacy endpoint in Arms A and B. It is defined as the proportion of patients with CR, PR, or SD as the response assessment at the 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).

The null and alternative hypotheses are set as follows:

H_0: Modified DCR = 40%

H_a: Modified DCR > 40%

A binomial exact test will be performed for hypothesis testing in each arm separately in the Safety Analysis Set. If the obtained one-sided p-value is < 0.025, it will be concluded that pamiparib combination therapy showed a statistically significant increase of modified DCR compared to historical control. Therefore, the superiority of pamiparib combination therapy will be demonstrated in this arm.

Two-sided binomial exact 95% confidence interval (CI) of modified DCR will be constructed to assess the precision of the rate estimate.

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

Sensitivity analysis of modified DCR will be carried out in the Efficacy-evaluable Analysis Set.

Phase 2 (Arm C)

ORR is the primary efficacy endpoint in Arm C. 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)

The null and alternative hypotheses are set as follows:

H_0: ORR = 10%

H_a: ORR > 10%

A binomial exact test will be performed similarly to that described for Arms A and B.

Secondary Efficacy Analysis:

Descriptive statistics will be used to summarize the secondary efficacy analysis.

DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR, or SD. BOR is defined as the best response recorded from the start of study treatment until data cutoff or start of new anti-cancer therapy.

CBR is defined as the proportion of patients with BOR of CR, PR, or durable SD (SD ≥ 24 weeks).

Exact 95% CIs will be calculated for the rate variables: ORR for patients with measurable disease at baseline, DCR and CBR in the Safety Analysis Set.

PFS is defined as the time from the date of first study treatment to disease progression or death, whichever occurs first.

PFS censoring rule will follow the FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2007). Patients who have a clinical determination of progression should undergo an MRI, if possible, to correlate radiographic findings with the clinical findings. Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient was known to be progression-free. Data for patients who started new anti-cancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy. More details will be provided in the statistical analysis plan.

DOR is defined as the time from the date of the earliest documented response to disease progression or death for any cause, whichever occurs earlier. Only responders will be included in the DOR calculation.

OS is defined as the time from the date of first study treatment to death from any cause.

Time-to-event variables PFS, DOR, and OS will be estimated using the Kaplan-Meier method in the Safety Analysis Set. Kaplan-Meier estimates of PFS, DOR, and OS will be plotted over time. Median PFS, DOR, and OS for each arm will be presented (if possible to estimate), along with their 2-sided 95% CIs using generalized Brookmeyer and Crowley method. The PFS-6m, OS-6m, and OS-12m, defined as the percentages of patients in the analysis population who remain alive and progression-free at 6 months (or alive at 6 or 12 months for OS-6m and OS-12m), will be estimated using Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula. OS will be assessed by 6-month intervals until the last patient enrolled on the study had died.

Selected efficacy endpoints will be summarized in the Efficacy-evaluable Analysis Set as sensitivity analysis.

In Phase 2, modified DCR (in Arms A and B) and ORR (in Arm C) will be summarized in the specified subgroups: sex, age group (<65 vs. ≥ 65 years of age), race, ECOG performance status (0 vs. ≥ 1), prior surgery status, baseline corticosteroid use, mutations, and geographic region. In addition, ORR (in Arm C) will be summarized by relapse status.

Pharmacokinetic Analyses:

Population PK analysis may be carried out to include plasma concentrations from this trial in an existing model. PK parameters such as minimum observed plasma concentration (C_{min}) will be summarized, and additional PK parameters such as apparent clearance of the drug from plasma (CL/F) and area under the plasma concentration-time curve from zero to 24 hours post-dose (AUC_{0-24}) may be derived from the population PK analysis if supported by data.

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

Exploratory Efficacy Analyses:

[redacted]

Safety Analysis:

Safety will be assessed by monitoring and recording of all AEs graded by CTCAE v4.03. Laboratory values (hematology, clinical chemistry, coagulation, and urinalysis), vital signs, physical examinations, and ECG findings will also be used in determining the safety of study treatment.

Sample Size:

Approximately 300 patients (60 in Phase 1b and 240 in Phase 2) may be enrolled. The actual sample size

in Phase 1b will depend on the number of cohorts enrolled per arm.

In Phase 2, the sample size calculation is carried out using modified DCR in Arms A and B and ORR in Arm C.

- Assuming modified DCR of 60% in Arms A and B vs. 40% in historical control, the power of a binomial exact test is 0.874 in each arm when n = 60.
- Assuming ORR of 25% in Arm C vs. 10% in historical control, the power of a binomial exact test is 0.847 when n = 60 per expansion cohort.

With the above assumptions, the binomial exact 95% CI of modified DCR is (46.5%, 72.4%) in Arms A and B and the binomial exact 95% CI of ORR is (14.7%, 37.9%) in each expansion cohort of Arm C.

Interim Analysis:

A brief data summary will be performed once the Phase 1b dose escalation portion is completed. In Phase 2, an interim analysis will be implemented in each arm after approximately the first 20 patients in that arm complete ≥ 2 tumor assessments. This analysis is for futility only. No recruitment stop is planned for this interim analysis. If the conditional or predictive power of demonstrating the final efficacy is < 10%, enrollment in this arm will be halted and safety and efficacy data will be further evaluated before making the decision of whether to stop the arm permanently. Otherwise, the enrollment will be continued to approximately 60 patients in this arm.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24h}	area under the plasma concentration-time curve from zero to 24 hours post-dose
BER	base excision repair
BGB-290	study drug code (also known as pamiparib)
BID	twice daily
BOR	best overall response
CBR	clinical benefit rate
CL	clearance
CL/F	apparent clearance
C_{min}	minimum observed plasma concentration
C_{max}	maximum observed plasma concentration
C_{trough}	lowest observed plasma concentration
CI	confidence interval
CR	complete response
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
DSB	Double-strand break
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
(e)CRF	(electronic) case report form
EDC	electronic data capture

EGFR	epidermal growth factor receptor
EOT	end-of-treatment
FDA	Food and Drug Administration
FLAIR	fluid attenuated inversion recovery
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	homologous recombination
IB	Investigator's Brochure
IC_{50}	half inhibitory concentration
ICH	International Conference of Harmonisation
ICF	informed consent form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IRF	Independent Radiology Facility
MAD	maximum administered dose
MedDRA	Medical Dictionary for Regulatory Activities
MGMT	O^6-methylguanine-DNA methyltransferase
MMR	Mismatch Repair
MRI	magnetic resonance imaging
MS-PCR	methylation-specific polymerase chain reaction
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
Pamiparib	BGB-290
PAR	poly(ADP-ribose)
PARP	poly(ADP-ribose) polymerase
PBMCs	peripheral blood mononuclear cells
PD	progressive disease

PFS	progression-free survival
PI3K	phosphatidylinositol-3-OH kinase
PK	pharmacokinetic(s)
PK/PD	pharmacokinetic/pharmacodynamic
PO	orally
PR	partial response
PT	Preferred Term
PTV	planning target volume
QD	once daily
QTc	QT interval corrected for heart rate
RANO	Response Assessment in Neuro-Oncology
RP2D	recommended Phase II dose
RT	radiation therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Class
SSB	single-strand break
TEAE	treatment-emergent adverse event
TMZ	temozolomide
TPR	Time Point Response
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Biology of Glioblastoma

Glioblastomas multiforme (GBM), the most aggressive subtype of gliomas, harbor a range of oncogenic mutations. These mutations are associated with resistance to both chemotherapy and radiation therapy (RT). A substantial number of these genetic alterations affect key players in DNA repair pathways.

- Methylation of the O^6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter and Mismatch Repair (MMR) gene mutations: *MGMT* promoter methylation was associated with a profound shift in the nucleotide substitution spectrum of treated GBMs. Notably, high occurrence of MMR gene mutations was observed in *MGMT*-hypermethylated tumors (Cancer Genome Atlas Research Network 2008).
- Downregulation of the p53 signaling pathway: Around 70% of GBM patients were reported to have somatic mutations affecting the p53 pathway. Inactivation of the p53 pathway was due to ARF deletion in 55%, MDM2 amplification in 11%, and MDM4 amplification in 4% of GBM patients (Cancer Genome Atlas Research Network 2008).
- Downregulation of the retinoblastoma (RB) signaling pathway: RB1 and its paralogs p107 and p130 play a central role in DNA double-strand break (DSB) repair by non-homologous end joining (NHEJ) (Huang et al 2015). A high frequency of mutations affecting the RB pathway was reported for GBM. The most common alterations were deletion of the CDKN2A and CDKN2B loci on chromosome 9p21 in 55% and 53% of the cases, respectively, followed by amplification of the CDK4 locus in 14% (Cancer Genome Atlas Research Network 2008).
- Upregulation of the epidermal growth factor receptor (EGFR)/Ras/phosphatidylinositol-3-OH kinase (PI3K) signaling pathway through PTEN alterations: PTEN alterations have been reported in 34% of GBM (Smith et al 2001). PTEN loss leads to defects in DNA DSB repair by homologous recombination (HR).

The high frequency of genetic alterations in GBM affecting DNA repair pathways suggests that DNA-damaging agents or agents interfering with DNA repair may be able to provide clinical benefit for GBM patients. This hypothesis is supported by the current standard of care for GBM patients but has not been adequately explored for other classes of drugs, such as inhibitors of poly(ADP-ribose) polymerase (PARP).

1.2. Imaging and Treatment of Glioblastoma

1.2.1. Overview and Key Data for Glioblastoma

GBM is the most common primary malignant brain tumor in adults with approximately 10,000 cases diagnosed annually in the United States (US) and with a dismal prognosis despite aggressive

treatment (CBTRUS 2012). Because of the infiltrative nature of GBM, surgery alone is never curative. Therefore, the majority of patients are subsequently treated with RT with or without chemotherapy. In 2005, Stupp and colleagues published a landmark study demonstrating a 2.5-month overall survival (OS) benefit with the addition of the alkylating agent temozolomide (TMZ) to surgery and RT (Stupp et al 2005). The results of this large trial established the role of TMZ, along with maximal safe resection and RT, for the treatment of newly diagnosed GBM patients <65 years old. Preliminary evidence that inactivation of the *MGMT* protein conferred sensitivity to TMZ (Esteller et al 2000; Hegi et al 2004) and TMZ's efficacy in recurrent glioma (Yung et al 2000) served as supporting data for this large, randomized, Phase 3 trial. Subset analyses confirmed improved survival and sensitivity to TMZ for tumors deficient in *MGMT* (defined by *MGMT* promoter methylation) compared to those with adequate *MGMT* expression (defined by an unmethylated *MGMT* promoter) (Hegi et al 2005).

Since the added benefit with use of TMZ is limited in the MGMT promoter unmethylated glioblastoma population, the risk-benefit ratio of combined modality treatment in these patients (eg, myelosuppression and an increased risk of pseudo-progression events) has been questioned. In contrast, a recently published randomized study of short-course radiation plus TMZ in elderly patients with GBM (Perry et al 2017) demonstrated the benefit of chemoradiotherapy in patients with either methylated or unmethylated *MGMT* status. Hence, significant regional debate remains with respect to whether incorporation of TMZ should be based upon *MGMT* methylation status alone (Newlands et al 1997, Stupp et al 2001). The current European Association for Neuro-Oncology guidelines for glioma do acknowledge the option of radiotherapy only for newly diagnosed *MGMT* promoter unmethylated glioblastoma. This reverses the older European Society for Medical Oncology guideline that reserved this option for patients treated within clinical trials (Weller et al 2017; Stupp et al 2014). More recently, several clinical trials evaluated an investigational agent in combination with RT but without TMZ in patients with newly diagnosed glioblastoma and unmethylated *MGMT* promoter (Wick et al 2016; Herrlinger et al 2016; Nabors et al 2015).

1.2.2. Imaging of Glioblastomas

An important aspect to the treatment of glioblastoma is appropriate imaging and detection of response. Standard-of-care GBM neuroimaging includes the following.

1. After initial primary debulking surgery, magnetic resonance imaging (MRI) of the brain without and with contrast can serve as baseline imaging prior to start of RT ± chemotherapy.
2. After surgery and RT, MRI of the brain without and with contrast is usually performed 2 to 6 weeks following completion of treatment, and then every 2 months.
3. During chemotherapy or a course of RT, MRI of the brain without and with contrast every 8 weeks is the usual approach. Standard-of-care surveillance MRI of the brain without and with contrast is then repeated every 3 months for 3 years, followed by every 6 months for an additional 2 years, and then annually.

Notwithstanding standardization of imaging, challenges in the neuroimaging evaluation of patients undergoing treatment for GBM remain. In particular, differentiating a treatment response from tumor progression can be problematic, and a validated neuroimaging method to clearly distinguish between pseudo-progression and tumor progression has unfortunately not been found to date.

In multicenter MRI studies, standardization of MR scanners and parameters (eg, field strength, gradient system, manufacturer, and sequences) must be considered. It is well known that even minor differences in hardware or sequence timing may result in significant changes in image contrast and analysis. Lesion contrast is also dependent on the magnetic field strength of the scanner, with higher field strengths showing higher contrast-to-noise compared with lower field strength scanners (eg, 3 T vs 1.5 T).

Ellingson and colleagues have provided recommendations for brain tumor MRI acquisition for use in multicenter clinical trials to reduce variability associated with response assessment (Ellingson et al 2015). The protocol was designed to allow flexibility in terms of adding subsequent imaging techniques, such as the addition of perfusion MRI prior to acquisition of post-contrast 3D T1-weighted images, the addition of susceptibility-weighted or gradient-echo acquisition before contrast injection, or acquisition of post-contrast, 2D T1-weighted turbo spin-echo (TSE) images following post-contrast 3D T1-weighted image acquisition.

1.2.3. O^6-methylguanine-DNA Methyltransferase Status and Treatment Response

1.2.3.1. Methylation of the O6-methylguanine-DNA Methyltransferase (*MGMT*) Gene Promoter

TMZ and other alkylating agents, including the nitrosoureas carmustine and lomustine, are commonly used cytotoxic chemotherapies for newly diagnosed and recurrent GBM. They induce apoptosis and cell death by methylating guanine at the O^6 position, initiating a DSB in the DNA and cell cycle arrest. The *MGMT* protein removes the damaging alkyl groups from the O^6 position of guanine and repairs the DNA. The alkylated protein is then degraded, requiring constant replenishment for DNA repair to be effective.

High expression of *MGMT* in cancer cells, including glioma cells, account for the predominant mechanism of resistance to alkylating agents. Consistent with this finding, lack of *MGMT* protein correlates with increased sensitivity to DNA-damaging agents, like temozolomide or XRT. The absence of *MGMT* protein in GBM has been determined to be almost exclusively caused by methylation of the promoter of the *MGMT* gene (Hegi et al 2005) referred to hereafter as '*MGMT* methylation' or 'methylated GBM.'

Conversely, patients with an unmethylated *MGMT* promoter or higher levels of *MGMT* protein in their tumors are less likely to respond to alkylating agents resulting in shorter survival compared with patients with a methylated *MGMT* promoter or lower levels of *MGMT* protein (Table 1).

It is known that *MGMT* is inactivated after each reaction (ie, suicide enzyme). Therefore, if the rate of DNA alkylation were to outpace the rate of *MGMT* protein synthesis, the enzyme could, in theory,

be depleted. Several studies have shown that prolonged exposure to TMZ can deplete *MGMT* activity in blood cells, a process that could potentially increase the antitumor activity of the drug (Brandes et al 2006; Gilbert et al 2013; Strik et al 2008; Tolcher et al 2003). This resistance to TMZ remains a critical barrier to the effective treatment of glioblastoma.

1.2.3.2. *MGMT* Methylation Status and Significance for Newly Diagnosed Glioblastoma

Despite differences in the diagnostic methods used to detect *MGMT* methylation, studies have consistently demonstrated improved outcomes for patients with methylated GBM regardless of treatment, showed added benefit with TMZ, and suggested that *MGMT* methylation is both prognostic and predictive (Table 1).

Table 1: **O^6-methylguanine-DNA Methyltransferase (*MGMT*) Status and Clinical Benefit in Newly Diagnosed Glioblastoma**

Study (Phase)	Age, median (range)	Treatment arm	PFS		OS	
			u*MGMT* (months)	m*MGMT* (months)	u*MGMT* (months)	m*MGMT* (months)
Stupp (Phase 3)	56 (19–71)	Radiation	4.4	5.9	11.8	15.3
		Chemotherapy	5.3	10.3	12.7	21.7
NOA-08 (Phase 3)	72 (66–84)	Radiation	4.6 (EFS)	4.6 (EFS)	10.4	9.6
		Chemotherapy	3.3 (EFS)	8.4 (EFS)	7	Not reached
Nordic (Phase 3)	70 (60–88)	Radiation	Not reported	Not reported	7.0	8.2
		Chemotherapy	Not reported	Not reported	6.8	9.7
ANOCEF (Phase 2)	77 (80–87)	Chemotherapy	2.6	6.0	4.4	7.2
Brandes (Phase 2)	68 (65–82)	Chemoradiation	9.5	22.9	13.7	Not reached
German Glioma Network (Observational)	74 (70–86.6)	Radiation	5.2	4.5	8.8	7.8
		Chemotherapy	0.5	6.8	2.6	7.2
		Chemoradiation	7.2	7.3	10.4	13.1
Perry et al (Phase 3)	73 (65–90)	Radiation Chemoradiation	Not reported	Not reported	7.9	7.7

Sources: General: Chen et al 2013; Stupp: Stupp et al 2005; NOA-08: Wick et al 2012; Nordic: Malmström et al 2012; ANOCEF: Gállego Pérez-Larraya et al 2011; Brandes: Brandes et al 2009; GGN: Weller et al 2009; Perry et al 2017.
EFS = event-free survival; m*MGMT* = methylated O^6-methylguanine-DNA methyltransferase promoter; OS = overall survival; PFS = progression-free survival; u*MGMT* = unmethylated O^6-methylguanine-DNA methyltransferase promoter

In several studies on improving treatment of patients with newly diagnosed GBM without *MGMT* promoter methylation (and thus little or no benefit at all of the addition of TMZ to be expected), TMZ has been left out of the investigational arm. Multiple European-led trials have used RT alone, rather than RT with chemotherapy, as the comparative arm in trials of novel targets to replace TMZ

(Herrlinger et al 2014; Wick et al 2014, Wick et al 2013). The GLARIUS trial, a randomized Phase 2 study of irinotecan, bevacizumab, and RT versus TMZ and RT in newly diagnosed unmethylated GBM found a significantly prolonged median progression-free survival (mPFS) of 9.7 months in the experimental arm versus 5.9 months in the standard arm (Herrlinger et al 2014). Despite the mPFS benefit observed in this study, the median overall survival (mOS) between the two groups was comparable (16.6 months compared with 17.3 months, respectively). This suggested that it is reasonable to omit TMZ in newly diagnosed unmethylated patients without adversely impacting the patients' survival (Herrlinger et al 2014).

1.2.3.3. *MGMT* Methylation Status and Significance for Recurrent Glioblastoma

In the recurrent setting, *MGMT* methylation status has yet to guide treatment. Preliminary data suggested that prolonged exposure to TMZ may suppress *MGMT* activity, therefore making the cells more susceptible than the standard 5-day regimen (Days 1 to 5 of a 28-day cycle) (Hegi 2005). This hypothesis led to a series of studies of dose-dense schedules to prevent repletion of *MGMT* and improve sensitivity to TMZ and shift the outcome of unmethylated GBM patients toward methylated GBM patients (Perry et al 2010; Weller et al 2010; Weller et al 2013). A large, randomized trial of dose-dense TMZ (21 days on and 7 days off at 100 mg/m^2) in the adjuvant setting (RTOG 0525) in newly diagnosed GBM patients resolved the conflicting data on timing of standard temozolomide and efficacy of alternative dosing. No improvement was seen in mPFS or mOS with dose-dense TMZ, regardless of *MGMT* promoter methylation status (Gilbert et al 2013). These findings, in addition to results from dose-dense TMZ at recurrence (Wick et al 2009) suggest that unmethylated tumors cannot be 'sensitized' to TMZ by solely intensifying the dose.

The standard dosing of TMZ (Days 1 to 5 of a 28-day cycle) has shown a favorable safety profile and modest efficacy in clinical trials. TMZ in increased dose density schedules in maintenance after RT and for recurrent tumors that have evaded from prior standard therapy that may include TMZ appears to be a rational approach.

1.2.4. Treatment Toxicity

The dose-limiting factor associated with chemotherapy for GBM is bone marrow toxicity. Daily, low-dose TMZ given concomitantly with RT rarely affects platelet or neutrophil counts, but patients usually experience some degree of lymphopenia. In contrast, the standard TMZ dosing and schedule (Stupp et al 2005) used for adjuvant treatment frequently causes neutropenia and/or thrombocytopenia.

To achieve clinical benefit, it is imperative that the magnitude of any sensitizing effect for TMZ is significantly greater in the tumor than in the critical normal tissues. Targeting DNA repair pathways might be predicted to achieve tumor-specific chemo- and/or radio-sensitization.

1.2.4.1. Toxicity of Dose-dense Temozolomide Regimens

Studies have been conducted to assess the safety concerns (Neyns et al 2010). The greater dose intensity achieved in these studies does not appear to significantly increase the frequency of

thrombocytopenia or neutropenia (Gilbert et al 2013). Available data from Phase 2 trials indicate a high incidence of lymphopenia (8% to 68%), a common TMZ toxicity, and a slight increase in fatigue. Grade 3 or 4 lymphopenia in trials using the 21 of 28 days TMZ schedule (75 mg/m^2) occurred in 24% to 53% of cases, and Grade 4 lymphopenia, which may increase the risk of opportunistic infections, was reported in 47% in one study for recurrent anaplastic astrocytoma or oligoastrocytoma (Neyns et al 2008).

In the RTOG 0525 study, adverse events (AEs) were evaluated separately during the concurrent chemo- and radiotherapy and the adjuvant treatment phase. Grade 3 or 4 lymphopenia was the most common toxicity occurring in 12% of patients but without significant opportunistic infections. Serious neutropenia and thrombocytopenia occurred in 3.6% and 6.8%, respectively, of all patients undergoing RT. There was one treatment-related death as a result of neutropenia (Gilbert et al 2013).

1.3. Background on Poly (ADP-ribose) Polymerase Inhibitors and Pamiparib (BGB-290)

1.3.1. Poly (ADP-ribose) Polymerase (PARP) and Pamiparib

Poly (ADP-ribose) polymerase (PARP) proteins are involved in deoxyribonucleic acid (DNA) replication, transcriptional regulation, and DNA damage repair. Inhibition of PARP converts common single-strand DNA breaks into double-strand breaks during DNA replication. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP-ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA (Leonetti et al 2012).

Small-molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effect by modulating the PARylation activity of PARP1/2 and trap PARP proteins on damaged DNA. In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses as a single agent in patients with BRCA1- or BRCA2-mutant tumors, while achieving a favorable safety profile. Olaparib and rucaparib are two PARP inhibitors that are approved as a single agent for patients with advanced ovarian cancer who have a germline mutation in the BRCA gene (Approved product prescribing information; available online).

Pamiparib (also known as BGB-290) is a highly potent and selective inhibitor of PARP1 and PARP2 with demonstrated brain penetrance in nonclinical studies (see Section 1.3.4.1). As such it has the potential to differentiate from other PARP inhibitors by combining potent PARP-trapping activity with significant brain penetrance. This brain penetrance is particularly relevant within a GBM population where few cytotoxic drugs have demonstrated efficacy, thought to be due, at least in part, to the blood-brain barrier preventing adequate delivery to these tumors.

1.3.2. PARP Inhibitors and Glioblastoma

As summarized in Section 1.1, GBMs have a high prevalence of genetic alterations affecting DNA repair pathways, raising the possibility that PARP inhibitors may be able to contribute to clinical benefit for GBM patients. Whereas this hypothesis has not been adequately explored in the clinic,

nonclinical data for one such alteration, PTEN loss, support the concept of synthetic lethality of PARP inhibition with other pathways aside from *BRCA1/2*. Deletions in chromosome 10 encompassing the PTEN gene have been frequently observed in GBM (Endersby and Baker 2008; Li and Ross 2007) and have been estimated to occur in about one third of GBMs (Huang et al 2015). PTEN is a lipid phosphatase with a role in dampening PI3K/Akt signaling, and PTEN loss results in PI3K/Akt pathway hyperactivation. However, PTEN also plays a role in the maintenance of genome stability as demonstrated using mouse embryonic PTEN-/- cells. This phenotype was related to a defect in the regulation of the expression of RAD51, an important HR component (Shen et al 2007). Synthetic lethality of PTEN loss and PARP inhibition is supported by data that the PARP inhibitor veliparib is very effective in reducing the survival of PTEN-/- human GBM cell lines, whereas astrocytes with the intact PTEN gene are less sensitive to veliparib. PTEN-deficient astrocytes and GBM cells were also more sensitive to the methylating agent N-methyl-N′-nitro-N-nitrosoguanidine (MNNG) with a mechanism of action very similar to TMZ (McEllin et al 2010). These data suggest that GBMs with defects in DNA repair pathways may be sensitive to PARP inhibition, in particular when combined with DNA-damaging agents.

1.3.3. PARP Inhibitors in Combination with Temozolomide or Radiation

PARP-1 and PARP-2 have a key role in the base excision repair (BER) of N-methylpurines (N7-methylguanine and N3-methyladenine) that are generated by TMZ. In the presence of a functional BER system these damaged bases are promptly repaired and limit TMZ cytotoxicity. The first step of the BER process is the excision of the modified base by N-methylpurine glycosylase (MPG) resulting in an apurinic/apyrimidinic (AP) site that is subsequently cleaved by apurinic/apyrimidinic endonuclease. The resultant DNA nicks are finally repaired by the coordinate intervention of PARP-1, DNA polymerase, XRCC1 and ligase III. Inhibition of PARP activity hampers PARylation of PARP-1 and PARP-2, interrupting the completion of the repair process mediated by BER (Kim and Wilson 2012). Combining PARP inhibition with DNA-damaging TMZ leads to increased DNA damage that results in apoptosis and/or growth arrest. Repeated treatments with TMZ and PARP inhibitors also downregulate transcription and delay recovery of BER components in tumor cells (Tentori et al 1999; Tentori et al 2001). This mechanism might further enhance the cytotoxic effects of TMZ combined with a PARP inhibitor.

Since the discovery of synthetic lethality of PARP inhibitors in *BRCA*-deficient cells, accumulation of unrepaired single-strand breaks (SSBs) resulting from catalytic PARP inhibition has been considered central to the mechanism of action of PARP inhibitors. More recently, it has been demonstrated that PARP inhibitors also trap PARP1- and PARP2-DNA complexes at DNA damage sites and that PARP trapping can be more cytotoxic than unrepaired SSBs (Kedar et al 2012; Murai et al 2012; Murai et al, 2014a; Fojo and Bates 2013). Murai and colleagues investigated whether PARP trapping is important for chemotherapy combinations that are currently being studied in the clinic. To this purpose, a PARP inhibitor with potent PARP-trapping activity, olaparib, was compared to a PARP inhibitor with similar catalytic PARP inhibition but significantly less PARP-trapping activity, veliparib. Both drugs showed highly synergistic effects with the toposisomerase I inhibitor camptothecin, consistent with catalytic PARP inhibition being important for the activity of

this combination. However, in combination with the alkylating agent TMZ, olaparib was significantly more effective than veliparib indicating that PARP trapping was essential for the combination activity (Murai et al 2014b). Gill and colleagues similarly showed that sensitivity to a PARP inhibitor was due to DNA-trapping activity and that TMZ-mediated potentiation of PARP inhibitor activity was associated with enhanced trapping of PARP1-DNA complexes (Gill et al 2015). These data suggest that combinations of TMZ with PARP inhibitors with potent DNA-trapping activity may be of particular interest.

In glioma cells, pharmacological modulation of PARP activity increased growth inhibition by TMZ in both p53-wild-type and p53-mutant glioblastoma cells and markedly lowered the TMZ IC_{50} to levels below the concentration of TMZ that can be detected in the plasma or brain of treated patients. The most pronounced effect was observed in tumor cells resistant to TMZ due to high *MGMT* levels or to MMR deficiency. In fact, in short-term primary cultures of glioma cells derived from surgical specimens, the enhancement of chemosensitivity to TMZ induced by a PARP inhibitor was especially evident in *MGMT*-proficient cells. Moreover, in an MMR-deficient glioma cell line, in which an *MGMT* inhibitor would have been ineffective, the combination of TMZ with the PARP inhibitor reverted resistance to the methylating compound (Tentori et al 2001; Tentori et al 2002; Tentori et al 2003). These data suggest that GBM patients who derive less benefit from current standard of care because of lack of *MGMT* promoter methylation may benefit from a combination regimen that includes a PARP inhibitor.

Several clinical studies have been conducted with PARP inhibitors (olaparib, rucaparib, and veliparib) in combination with TMZ. To determine the maximum tolerated dose (MTD) in these studies, TMZ was administered at standard doses (135 to 150 mg/m^2/day or up to 1000 mg/m^2/month) with increasing doses of the PARP inhibitor. All studies experienced the challenge of significant myelosuppression as dose-limiting toxicities (DLTs), and observed anti-tumor activity was only modest (Gabrielson et al 2015; Gojo et al 2017; Hussain et al 2014; Middleton et al 2015; Plummer et al 2013; Su et al 2014). This is contrasted by a recent study for talazoparib, a PARP inhibitor with very good DNA-trapping activity. Standard doses of talazoparib (0.5 to 1 mg) were administered with low doses of TMZ in patients with non-*BRCA1/2*-mutated cancers (Wainberg et al 2016) The starting dose of TMZ was 25 mg/m^2, approximately 12.5% of the therapeutic dose, and the MTD was determined as 1 mg talazoparib plus 37 mg/m^2 of TMZ. This regimen was better tolerated than reported for prior studies, with less thrombocytopenia and neutropenia. Furthermore, promising efficacy was observed with 11 patients (61%) experiencing either a partial response or stable disease. These preliminary clinical results are in support of the hypothesis that PARP inhibitors with strong DNA-trapping activity may only require relatively low TMZ dose levels to exert their anti-tumor activity.

Ionizing radiation used in the clinical treatment of GBM generates mostly SSBs and to a minor extent DSBs. Single-strand breaks are repaired through the BER pathway, operating via either the *short patch* or the *long patch* repair sub-pathways, which differ in the size of the repair patch and the enzymes involved. A PARP-1 role in the *short patch* is well established, but its contribution in the *long patch* is still unclear. In non-replicating cells, PARP inhibition only delays the repair of SSBs

induced by radiation with a minimal impact on cell survival. On the contrary, PARP inhibition markedly enhances radiosensitivity of proliferating cells since unrepaired SSBs collide with the DNA replication machinery, generating DSBs. Thus, PARP inhibitors have the potential to increase the anti-tumor effect of RT by preventing DNA damage repair and increasing cytotoxic DNA damage (Godon et al 2008; Noel et al 2006; Dungey et al 2008).

1.3.4. Nonclinical Data for Pamiparib

1.3.4.1. Nonclinical Safety Data

The nonclinical toxicity and toxicokinetic profile of pamiparib was characterized in single and up to 91-day repeat-oral-dose studies in rats and dogs, and in a core battery of genotoxicity tests, including in vitro Ames and chromosomal aberration assays, and in vivo bone marrow micronucleus assays in rats. Safety pharmacology assessments included in vitro hERG channel activity assays and in vivo studies of cardiovascular function in dogs, as well as central nervous system and respiratory system function tests in rats.

The main toxicity findings were bone marrow inhibition that correlated with clinical pathology changes and gastrointestinal toxicity that presented as emesis, decreased food consumption and decreased body weight. The systemic exposure increased dose-proportionally without apparent sex differences or accumulation. The MTD was considered to be 6 mg/kg in rats and 3 mg/kg in dogs for both 28-day and 91-day toxicity studies.

Pamiparib was not mutagenic in the *in vitro* Ames (bacterial reverse mutation) assay, but clastogenic in the *in vitro* chromosomal aberration assay in mammalian Chinese hamster ovary cells and in the *in vivo* bone marrow micronucleus assay in rats, which is consistent with its mechanism of action. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation and DNA damage repair. Pamiparib interacts with and inhibits the enzymatic repair machinery that carries out detection and repair of single-strand DNA breaks (SSBs).

In the general toxicity studies in rats and dogs, no gross lesions or histopathological changes were noted in male and female reproductive organs. No embryo-fetal toxicity studies were conducted or planning as it was not considered essential because of its genotoxicity and bone marrow inhibition.

There was no apparent inhibition of pamiparib on hERG channel as the value of half-maximal inhibition concentration (IC_{50}) was 12.4 μM; for comparison, the IC_{50} of the positive control amitriptyline was 1.9 μM. No effects on blood pressure, heart rate or ECGs were noted in telemetry-instrumented conscious dogs. No effects on the central nervous system or respiratory functions were noted in Sprague-Dawley rats. No abnormal changes in the cardiovascular, central nervous system, and respiratory system were identified in single- or repeat-dose toxicity studies in both rats and dogs. No QT interval prolongation was noted in cardiovascular function studies in conscious dogs and in 28-day and 91-day repeat-dose toxicity studies in dogs. Embryo-fetal toxicity studies were not conducted because of the already established genotoxicity of and bone marrow inhibition by pamiparib.

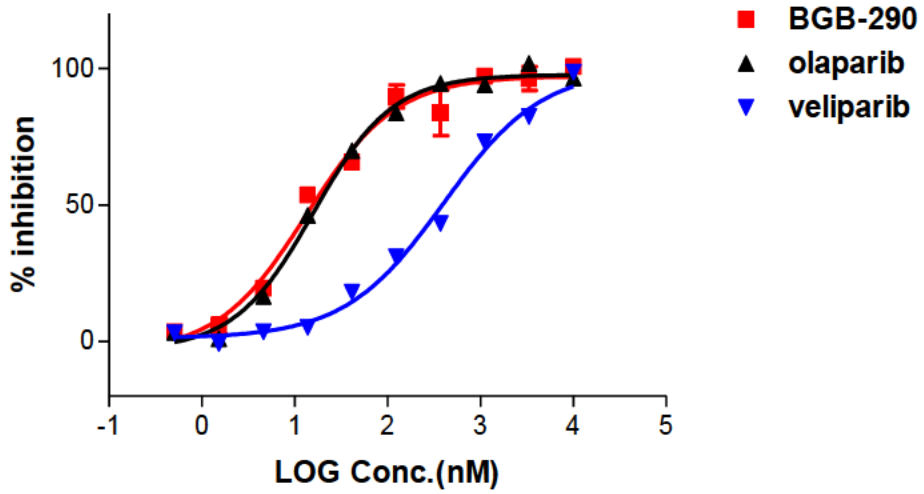
In summary, all available toxicological studies and data are adequate to support clinical development of pamiparib for treatment of patients with advanced cancer. For additional nonclinical information, please refer to the most current version of the pamiparib Investigator's Brochure (IB).

1.3.4.2. Nonclinical Activity Data

DNA-trapping Activity of Pamiparib

A subset of PARP inhibitors is able to trap PARP enzymes at damaged DNA sites, and these trapped PARP-DNA complexes appear to be more cytotoxic than unrepaired DNA breaks caused by PARP inactivation (Section 1.3.3). The DNA-trapping activity of pamiparib was measured by a fluorescence polarization (FP) binding assay. Fluorescence-labeled nicked DNA was pre-incubated with PARP; inhibitors and then NAD were added to initiate the PARylation reaction. PARylation reduced the FP signal by freeing the DNA from PARP1. The potency of PARP inhibitors to trap PARP1-DNA complexes was derived from measuring the FP signal as a function of compound concentration. Pamiparib showed potent DNA-trapping activity (with IC_{50} of 13 nM), similar to olaparib and 30-fold more potent than veliparib (Figure 1).

Figure 1: DNA-Trapping Activity of Pamiparib and Other PARP Inhibitors



Compound	BGB-290	olaparib	veliparib
EC_{50} (nM)	13	16	400

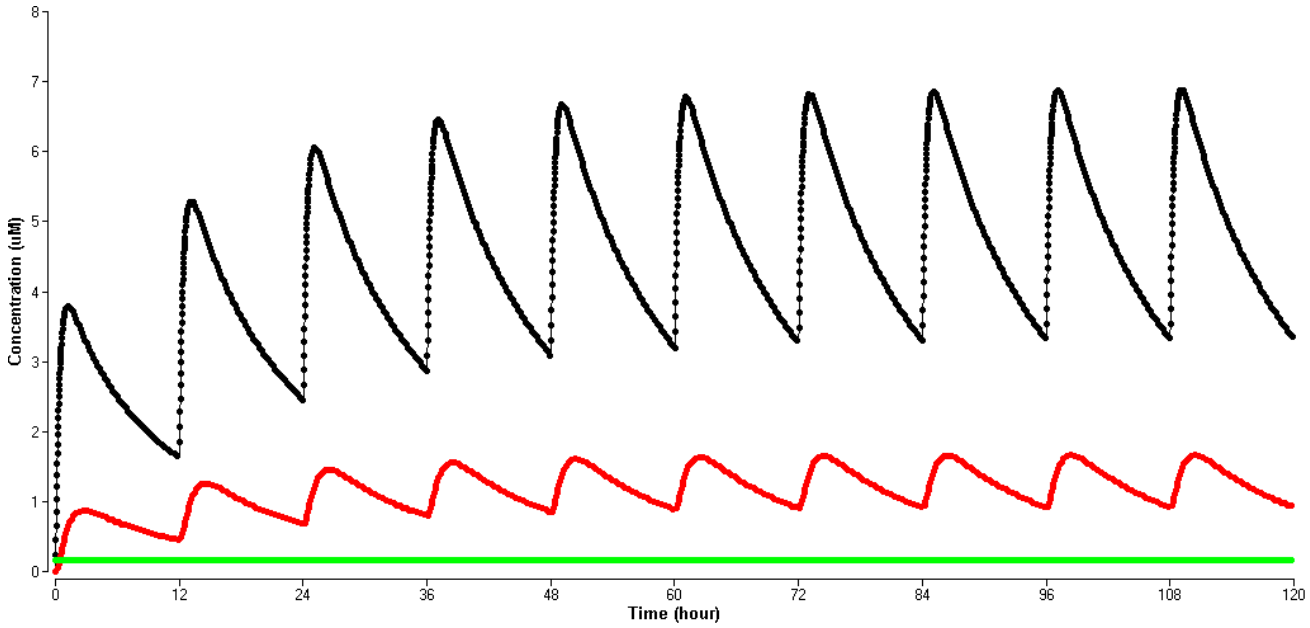
Brain Penetration of Pamiparib

The brain penetration of pamiparib in male C57/b6 mice was evaluated after a single oral administration of pamiparib (10 mg/kg). The individual brain/blood concentration ratio was calculated to be 18.7%, 18.9% and 19.5% at 1, 2 and 4 h, respectively. The mean brain/blood

concentration ratio calculated by partial area under the concentration-time curve ($AUC_{1\sim4h}$) was 18%. In a tissue distribution study in rats, pamiparib was detected in all organs checked after oral administration. Specifically, in individual rat brains, the ratio of brain to blood concentration ranged from 21% to 63% over time (0.5 to 24 hours) with a mean brain/blood ratio ($AUC_{1\sim4h}$) of 26%.

A population pharmacokinetic/pharmacodynamic (PK/PD) model was developed based on clinical PK data from Phase 1 trial BGB-290-AU-002 (Section 1.3.5) and tissue distribution data from rats. Simulated brain concentration-time profiles in a typical patient suggested that trough brain concentration at 60 mg BID was above the threshold of 0.5 µM identified from a sensitive animal model for efficacy (Figure 2).

Figure 2: Simulation of Pamiparib Concentrations in Human Organs



Simulated PK profiles:

bottom profile in red = brain;

top profile in black = plasma;

horizontal green line = threshold of 0.5 µM identified from a sensitive animal model for efficacy

Single-Agent Antitumor Activity of Pamiparib

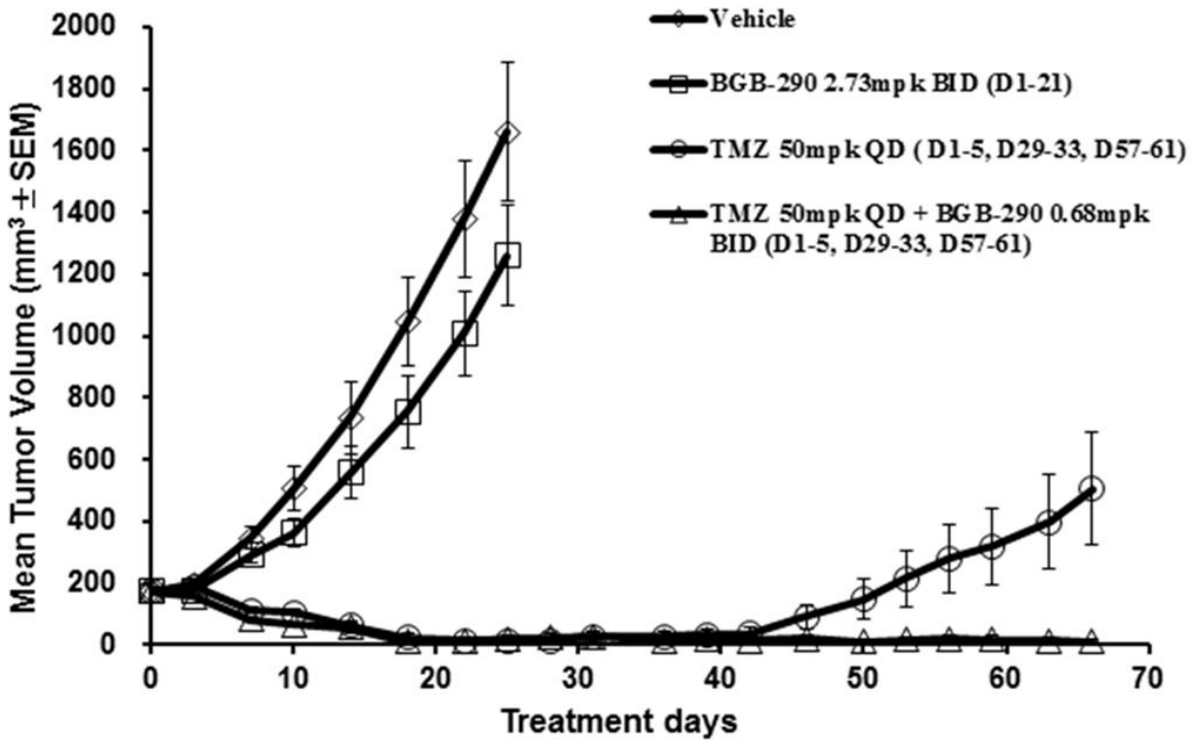
Pamiparib as a single agent has demonstrated excellent in vitro activity against tumor cell lines with defects of the HR pathway. In vivo, pamiparib showed strong antitumor activity against a BRCA1-mutant mouse xenograft model (MDA-MB-436 breast cancer) and was 16-fold more potent than olaparib. In a PK/PD study, oral (PO) administration of pamiparib resulted in time- and dose dependent inhibition of PARylation in MDA-MB-436 breast cancer xenografts in mice.

Inhibition of PARylation in the tumor tissues correlated well with tumor drug concentrations of pamiparib.

Combination Antitumor Activity of Pamiparib with Temozolomide

The anti-proliferative effect of pamiparib in combination with TMZ was evaluated in 8 human GBM cell lines resistant to single-agent TMZ (EC_{50} of 32 μM or greater). In 7 of 8 cell lines, pamiparib demonstrated synergism with TMZ with a shift in EC_{50} for TMZ of 5-fold or greater. This synergism was also demonstrated in vivo in an H209 small cell lung cancer xenograft model (Figure **3**). Pamiparib (2.73 mg/kg BID x 21 days) as single-agent treatment had no significant effect on tumor growth. TMZ (50 mg/kg QD, Days 1-5 of each 28-day cycle) as single-agent treatment was quite effective in this model resulting in objective responses in all animals (1 PR and 7 CRs in 8 animals) after the first cycle of treatment. However, 6 of these 8 animals developed TMZ resistance after 3 cycles of treatment, and the mean tumor volume reached 505 mm^3 on Day 66. Addition of pamiparib (0.68 mg/kg BID, Days 1-5 of each 28-day cycle) resulted in objective responses in all animals (2 PRs and 6 CRs in 8 animals) after the first cycle of treatment. After completion of 3 cycles of treatment (on Day 66), most animals were still tumor-free (6/8), and the mean tumor volume was 12 mm^3. Thus, the combination of pamiparib and TMZ significantly enhanced TMZ antitumor activity and delayed resistance.

Figure 3: Combination Activity of Pamiparib and Temozolomide in H209 Small Cell Lung Cancer Xenograft Model

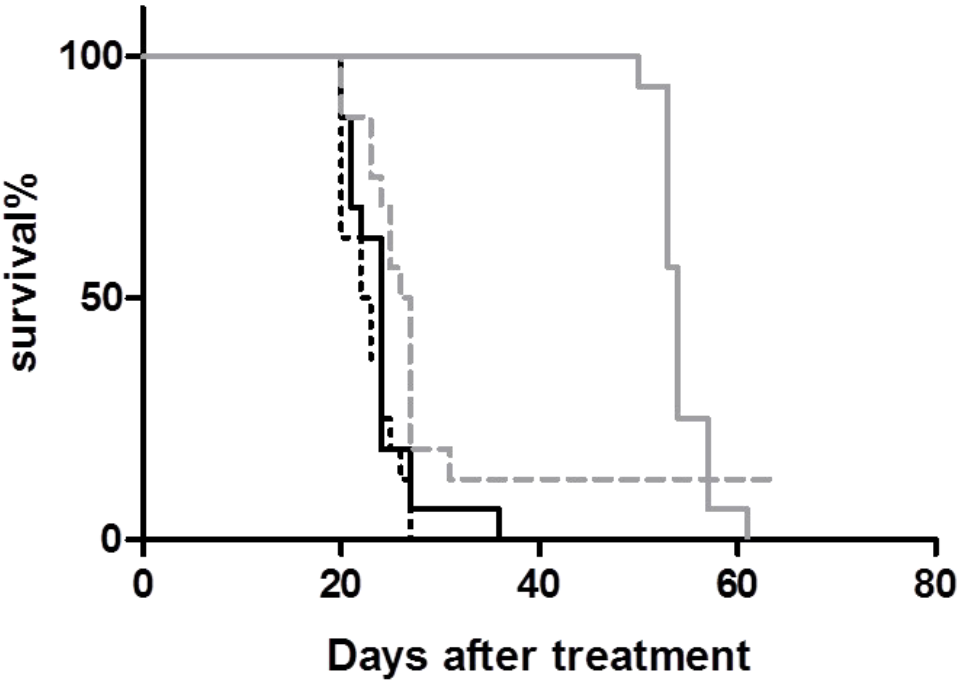


Diamonds = vehicle; squares = pamiparib 2.73 mg/kg twice per day on Days 1 to 21; circles = temozolomide 50 mg/kg

once per day on Days 1 to 5, Days 29 to 33 and Days 57 to 61; triangles = temozolomide 50 mg/kg once per day and pamiparib 0.68 mg/kg twice per day on Days 1 to 5, Days 29 to 33 and Days 57 to 61

Given the significant brain penetrance of pamiparib, its activity was further explored in an intracranial tumor model in nude mice for H209-T small cell lung cancer xenografts (Figure 4). H209-T is a TMZ-resistant cell line generated by treating H209-xenografted tumors with multiple cycles of TMZ in vivo. In this model, pamiparib (2.73 mg/kg BID) as single-agent treatment had no significant effect on tumor growth, with a median survival of 24 days compared to median survival of 22.5 days in the vehicle-treated group. H209-T intracranial xenografts showed resistance to the TMZ treatment alone (50 mg/kg), with median survival of 26.5 days. However, the combination of pamiparib and TMZ significantly prolonged animal survival compared to TMZ ($p<0.01$), with median survival of 54 days. The result suggests pamiparib in combination with TMZ can overcome TMZ resistance in this intracranial model.

Figure 4: Combination Activity of Pamiparib and Temozolomide in H209-T Intracranial Model



Dashed black line = vehicle; solid black line = pamiparib 2.73 mg/kg twice daily; dashed gray line = temozolomide 50 mg/kg once per day for 5 days; solid gray line = temozolomide 50 mg/kg once per day and pamiparib 0.68 mg/kg twice per day on Days 1 to 5, Days 15 to 19 and Days 29 to 33

1.3.5. Clinical Data for Pamiparib

Pamiparib is currently being studied in two Phase 1a studies (BGB-290-AU-002 in Australia, n = 53 [as of 30 September 2016] and BGB-290-102 in China, n = 15 [as of 25 September 2017]), as well as one Phase 1 study (BGB-A317/BGB-290_Study_001) for the combination of pamiparib with BGB-A317, an anti-PD-1 antibody (n = 41 [as of 02 February 2017]); one Phase 1b study

(BGB-290-103) for the combination of pamiparib with TMZ in patients with solid tumors (n = 10 [as of 01 December 2017]); and one Phase 1b/2 study (BGB-290-104) for the combination of pamiparib with RT and/or TMZ in patients with glioblastoma (n = 4 [as of 02 February 2017]). The study data from BGB-290-AU-002 are the most mature and key interim results are summarized below.

1.3.5.1. Pharmacokinetics Data for BGB-290-AU-002

In the first in human Phase 1 study, interim PK data of pamiparib showed that pamiparib is rapidly absorbed and eliminated after oral administration. The maximum serum concentration (C_{max}) and the drug exposure (AUC) increased in a nearly dose-proportional manner from 2.5 mg BID to 120 mg BID both after the single dose administration and at the steady state. The terminal half-life was determined to be approximately 13 h, with a range of 5.4 to 34 hours. At the steady state, from 2.5 mg BID to 120 mg BID, drug exposure was increased in a dose-dependent manner, with approximately 2-fold accumulation.

The impact of administration of a high-fat meal on the PK of pamiparib after a 60-mg dose is being assessed. Preliminary data from 13 patients enrolled in the food effect cohort of study BGB-290-AU-002 show that after administration with a high-fat meal, the rate of absorption was slower, as indicated by a delay in time to maximum concentration (T_{max}) from 2 to 7 hours, and lower maximum concentration (C_{max}), and $AUC_{0-\infty}$ after a high-fat meal was 15% lower than fasted (Table 2).

Table 2: PK Parameters for the Food Effect Cohort

PK Parameter	Fed (N = 13)	Fast (N=13)	Treatment Comparison GMR (90% CI)
AUC [ng•h/mL], Geo mean (CV, %)	25003 (58)	29419 (62)	0.85 (0.74 - 0.98)
C_{max} [ng/mL], Geo mean (CV, %)	1185 (32)	2013 (32)	0.59 (0.53 - 0.66)
T_{max} [h], Median (range)	7.0 (2.0 - 7.1)	2.0 (1.0 - 4.1)	
$T_{½}$ [h], Geo mean (range)	12.6 (5 - 22)	12.4 (5 - 23)	

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum observed concentration; CV = coefficient of variation; GMR, geometric mean ratio; h, hours; $T_{1/2}$, terminal half-life; T_{max}, time to maximum concentration

Based on pharmacodynamic data, with an apparent flat exposure-response for PAR inhibition and objective responses observed at lower dose levels, the decrease in C_{max} and the modest decrease of 15% in overall exposure with high-fat meal is not considered to be clinically significant. However, since pamiparib is not a substrate to known active transporters, and its brain penetration is thought to be driven by passive diffusion through a concentration gradient, in a brain tumor population where brain pentrance is key, the reduction in C_{max} may reduce brain penetration of pamiparib. Therefore, in GBM studies, patients will continue to be required to fast for 1 hour before and 2 hours after pamiparib administration.

1.3.5.2. Exploratory Biomarker Data

1.3.5.3. Clinical Safety and Preliminary Efficacy for BGB-290-AU-002

BGB-290-AU-002 is a first-in-human trial evaluating pamiparib to characterize the safety, the MTD, preliminary anti-tumor activity and the pharmacokinetics of pamiparib given as a monotherapy in a 3+3 dose escalation scheme. Pamiparib was administered in doses ranging from 2.5 mg PO BID up to 120 mg PO BID.

The study is being conducted in 5 Australian study centers, and preliminary data for 45 patients are available (cutoff date of 30 September 2016).

The preliminary safety data indicate that the most frequent adverse events (AEs) (≥ 10% of patients) assessed as related to pamiparib were nausea (58%, n = 26), vomiting (51%, n = 23), fatigue (29%, n = 13), diarrhea (18%, n = 8), dry mouth (16%, n = 7) and decreased appetite (11%, n = 5).

Hematologic AEs are of interest in this study. The most frequent hematologic AEs (≥ 10% of patients) assessed as related to pamiparib were anemia (22%, n = 10) and neutropenia (11%, n = 5).

Hematologic AEs, regardless of relatedness, were reported in 40% of patients (n = 18). Anemia was most frequent (33%, n = 15), followed by neutropenia (11%, n = 5) and thrombocytopenia (2%, n = 1).

Twenty-six patients experienced Grade 3 AEs (regardless of relatedness), and no Grade 4 AEs were reported. Eleven Grade 3 AEs in 9 patients (20%) were considered related to pamiparib: anemia (n = 5), neutropenia (n = 3), hypophosphatemia (n = 1), nausea (n = 1) and fatigue (n = 1). Serious AEs (SAEs) reported as related to pamiparib included anemia (n = 2) and nausea (n = 1).

SAEs were reported in 25 patients, and for 3 patients they were considered related to BGB 290: anemia (n = 2) and nausea (n = 1). Three patients discontinued study drug because of an AE: vomiting (n = 1), oral paresthesia (n = 1), and right neck cutaneous metastases (n = 1).

Four patients experienced a fatal AE ≤ 28 days after the last pamiparib dose. All deaths were due to complications of the underlying malignancy, and none was considered related to pamiparib.

Four patients experienced AEs that were considered DLTs: Grade 2 nausea that persisted despite optimal standard medical therapy in 2 patients; Grade 2 anorexia and Grade 2 nausea in 1 patient, and Grade 2 nausea and Grade 2 paresthesia in 1 patient. Based on the encountered DLTs and the overall safety profile of BGB-290, the MTD of BGB-290 was determined to be 80 mg PO BID (160 mg/day).

Ten patients achieved either a CR (n = 2) or PR (n = 8) responses; all responses were observed in patients with gynecological cancers, and responses were observed in the lowest dose cohorts (2.5 mg BID).

1.3.5.4. Pamiparib Dose Selection

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose of pamiparib 60 mg PO BID was selected using available clinical data from Study BGB-290-AU-002 (Section 1.3.5.3). The study determined the MTD of pamiparib to be 80 mg PO BID (160 mg/day). The dose of 60 mg BID was selected for further evaluation based on the following findings:

- A linear PK profile observed up to 80 mg BID
- Similar toxicity profiles at 60 mg and 80 mg BID with the following exceptions:
    - Fewer patients at 60 mg BID experienced treatment-related treatment-emergent adverse events (TEAEs) of anemia and neutropenia.
    - There was a slightly higher rate of dose interruptions at 80 mg vs 60 mg BID for anemia and nausea.
- Responses were observed across the dose range evaluated.

For additional and updated clinical information to date, please refer to the most current versions of the Pamiparib IB.

1.4. Study Rationale

Aside from surgical resection and RT as main standards of care, TMZ is the only systemic agent approved for first-line patients but only patients with methylated *MGMT* promoter benefit from TMZ. Glioblastomas have a high prevalence of alterations affecting DNA repair. There is strong scientific rationale that PARP inhibitors may provide antitumor activity in GBM, in particular when combined with standard-of-care DNA-damaging RT and/or TMZ. These novel combinations may furthermore be able to overcome resistance in GBMs with unmethylated *MGMT* promoter.

Pamiparib is a promising PARP inhibitor to study in GBM as it is a potent and selective inhibitor of PARP1 and PARP2, exhibits excellent DNA-trapping activity and shows brain penetrance in nonclinical experiments. In the clinic, pamiparib has shown favorable PK properties, has been well-tolerated and achieved maximum pharmacodynamic target modulation in PBMCs at a dose level well below the regimen for this study (10 mg versus 60 mg BID). PK modeling predicts that the 60 mg pamiparib dose will achieve brain concentrations required for antitumor activity. Nonclinical and preliminary clinical data suggest that maximizing PARP inhibition with lower doses of TMZ to induce DNA damage may provide antitumor activity with an acceptable safety profile. For these reason, the regimens of this study will try to maximize brain penetrance and PARP inhibition in tumor tissue by investigating full dose pamiparib with lower TMZ dose levels. In summary, pamiparib is an excellent candidate to determine the effects of combining PARP inhibition with RT and/or TMZ in this unmet medical need.

1.5. Risk-Benefit Assessment

Pamiparib has been studied in nonclinical toxicity and Phase 1 clinical studies. Pamiparib toxicities are largely consistent with the safety profile shared by other PARP inhibitors with the important exception that pamiparib may cause less myelosuppression.

PARP inhibitors, including pamiparib, show at least partial overlap with the safety profile of RT and/or TMZ. Therefore, patients of this study may experience AEs typical for these study treatments at a higher frequency and/or severity. In addition, patients may encounter AEs that are uniquely caused by the novel combination(s). Given the dire prognosis of GBM patients and the limited treatment options, the risk of combining pamiparib with RT and/or TMZ appears acceptable in the context of a Phase 1 study with close monitoring through AE reporting, recording of vital signs and ECGs, clinical laboratory testing and tumor assessments. As outlined in Sections 1.3 and 1.4, scientific rationale and supportive data are strong for combining PARP inhibitors with RT and/or TMZ in GBM. This warrants evaluation of these combinations in GBM patients, as the overall risk-benefit assessment appears favorable.

1.6. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and regulatory authorities, and in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES

2.1. Primary Objectives

2.1.1. Phase 1b

Arm A (pamiparib + RT): Patients with first-line glioblastoma with unmethylated *MGMT* promoter (unmethylated GBM)

- To assess safety and tolerability of pamiparib combined with RT
- To identify DLTs and determine the MTD or maximum administered dose (MAD) 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 MTD/MAD of pamiparib as determined in Arm A
- To select the RP2D for TMZ when combined with RT and the MTD/MAD of pamiparib determined in Arm A

Arm C (pamiparib + TMZ): Patients 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

2.1.2. Phase 2

Arm A, Expansion 1 (pamiparib + RT): Patients with first-line unmethylated GBM

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

Arm B, Expansion 1 (pamiparib + RT + TMZ): Patients with first-line unmethylated GBM

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

Arm C, Expansion 1 (pamiparib + TMZ): Patients with recurrent/refractory unmethylated GBM

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

Arm C, Expansion 2 (pamiparib + TMZ): Patients with recurrent/refractory methylated GBM

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

2.2. Secondary Objectives

Phase 1b, all Arms

- To 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, all Arms

- 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

2.3. Exploratory Objectives

[redacted]

3. STUDY ENDPOINTS

3.1. 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 only) 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, Arm A (pamiparib + RT) and Arm B (pamiparib + RT + TMZ)

- Modified disease control rate (DCR) as assessed using the Response Assessment in Neuro-Oncology (RANO) criteria (Appendix 2)

Phase 2, Arm C (pamiparib + TMZ)

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

3.2. Secondary Endpoints

Phase 1b, all Arms

- PK parameter for pamiparib of 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), PFS, and OS

Phase 2, Arm A (pamiparib + RT) and Arm B (pamiparib + RT + TMZ)

- ORR 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
- 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 parameter for 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 parameter for pamiparib: C_{trough}

3.3. Exploratory Endpoints

[redacted]

4. STUDY DESIGN

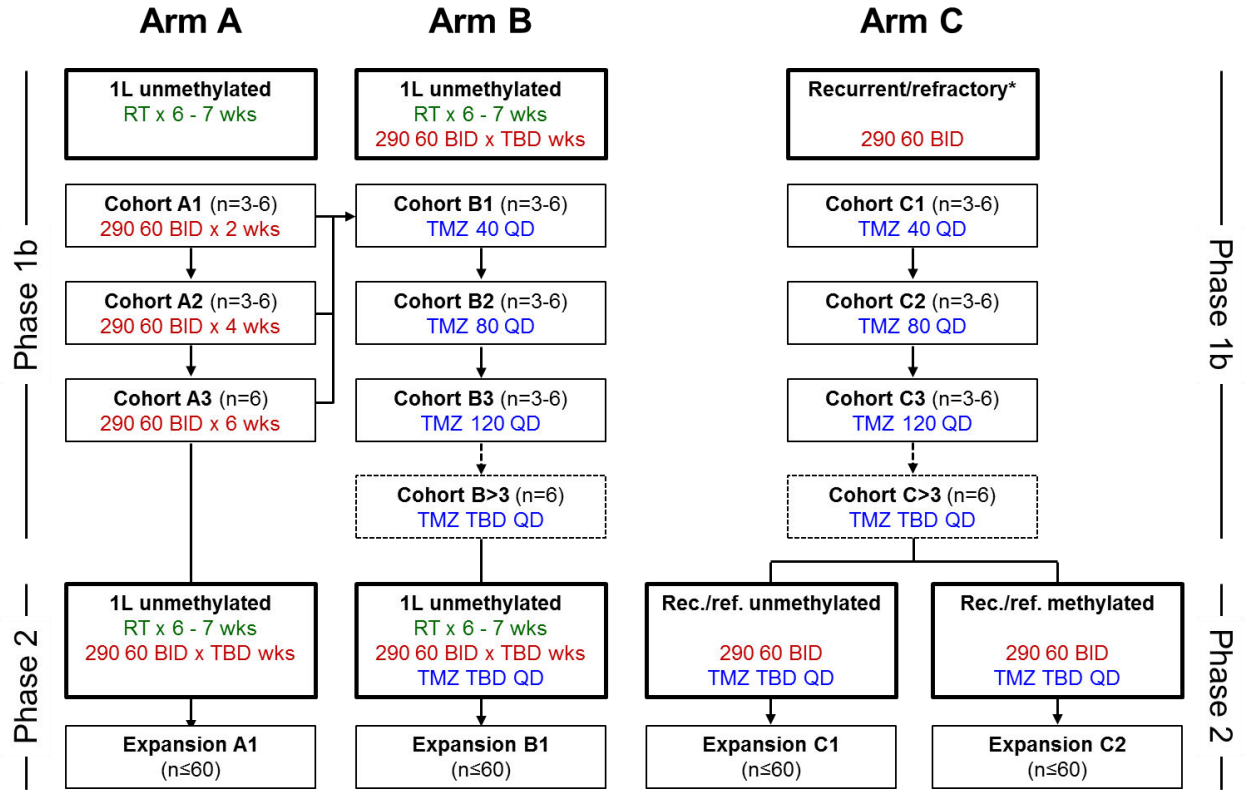
4.1. Summary of Study Design

This is an open-label, multi-center, multiple-dose, dose-escalation Phase 1b/2 study to determine the safety, pharmacokinetics (PK) and pharmacodynamics of pamiparib in combination with RT and/or

TMZ. Two initial arms (Arms A and C) and a potential third arm (Arm B) will be enrolled in the study (Figure 6). 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.

Patients will continue receiving pamiparib in combination with RT and/or TMZ until progressive disease (PD), unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor.

Figure 6 Phase 1b/2 Study Overview for Pamiparib with Radiation Therapy and/or Temozolomide in Patients with First-Line or Recurrent/Refractory Glioblastoma



* During dose escalation (Phase 1b), both unmethylated and methylated GBM are allowed in Arm C.
290 = pamiparib; 1L = first-line; methylated = glioblastoma with methylated *MGMT* promoter; rec./ref. = recurrent/refractory; RT = radiation therapy; TBD = to be determined; unmethylated = glioblastoma with unmethylated *MGMT* promoter; wks = weeks

4.1.1. Dose Escalation Phase (Phase 1b)

The Phase 1b, dose escalation phase consists of the following:

Arm A: Pamiparib (60 mg BID) administered continuously at increasing exposures of 2, 4, and 6 weeks in combination with RT administered for 6 to 7 weeks.

Arm B: Depending on the safety of the Arm A combination, the following combination may be explored: pamiparib (at the exposure determined as safe in Arm A) in combination with RT administered for 6 to 7 weeks and increasing doses of TMZ (Section 4.2.1).

In both Arms A and B, after RT is completed, patients will receive no further RT.

Maintenance Treatment for Arms A and B

Following completion of RT, at the discretion of the investigator and after discussion with the medical monitor, patients in the Arm A escalation and expansion and patients in Arm B escalation phases of the study may continue to receive pamiparib in combination with TMZ. TMZ will be given at a dose level lower than or equal to a dose that has been determined to be safe and tolerable in Arm C of study.

In the Arm B expansion phase of the study, maintenance treatment with pamiparib in combination with TMZ will be mandatory for all patients.

Dosing for this maintenance treatment should begin after the 4-week rest period (+ 7 days) to allow for recovery from RT treatment (please refer to Appendix 1 Table 4).

Arm C: Pamiparib (60 mg BID, administered continuously) in combination with increasing doses of TMZ (Section 4.2.1). TMZ will be administered on Days 1 to 21 of each 28-day cycle.

Approximately 60 patients may be enrolled in the 3 arms of the dose escalation phase. The actual sample size in this phase will depend on the number of dose escalation cohorts enrolled per arm.

4.1.2. Dose Expansion Phase (Phase 2)

Once the safety, tolerability, PK, pharmacodynamic, and preliminary antitumor activity have been reviewed for the dose escalation cohorts of each of the arms, up to approximately 60 patients may be enrolled in expansion cohorts for each of the 3 arms at a dose level below or equal to the MTD or MAD for that arm. In Arm C, 2 expansion cohorts may be opened, one for unmethylated GBM and one for methylated GBM (Section 4.3).

Approximately 60 patients may be enrolled during the dose escalation phase, and in each of the 4 dose-expansion cohorts totalling 240 patients in the dose expansion phase, for an approximate total of 300 patients enrolled in the entire study.

Adverse events (AEs) during and after the treatment period with study drug(s) will be followed and documented as outlined in Section 8.4 and Section 10. AEs will be graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) v4.03.

To determine the PK properties of pamiparib, blood samples will be taken at various time points as outlined in Section 8.5 and Appendix 1. To determine pharmacodynamic effects of pamiparib, blood samples will be obtained coinciding with specific PK time points as outlined in Section 8.5 and Appendix 1.

Disease status will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria (Appendix 2). Patients will undergo tumor assessments at screening and then every 8 weeks, or as clinically indicated.

In Arm B expansion phase of the study, maintenance treatment (pamiparib in combination with TMZ) will be mandatory for all patients. In Arm A expansion phase of the study, continuation of treatment (with pamiparib in combination with TMZ) will be at the discretion of the investigator after discussion with the Medical Monitor.

Following completion of RT, all patients in Arms A and B who continue on pamiparib in combination with TMZ should follow the schedule of assessments for maintenance treatment (Appendix 1 Table 4).

Patients in Arms A and B who have completed all study treatments per protocol and do not continue on pamiparib in combination with TMZ (maintenance) should have their EOT visit at the end of the Rest Phase, 28 days after RT was completed, unless they do not complete the full study treatment; in such a case, they should have the end-of-treatment (EOT) visit within 7 days of stopping all study treatment.

All other patients who have discontinued all study treatments should return to the clinic for an EOT visit within 7 days of stopping all study treatment. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization.

After the EOT visit, all patients should have regular follow-up for safety, efficacy, and survival as outlined in Section 6.6.

Study procedures and assessments are further detailed in Section 8.

4.2. Details of Dose-Escalation Stage

4.2.1. Starting Dose and Dose-Escalation Approach

Arm A

RT will be administered QD × 5 days/week for 6 to 7 weeks with 1.8 or 2 Gy/fraction for a total target dose of between 58 Gy and 64 Gy.

The starting dose for pamiparib will be the 60 mg PO BID based on the rationale outlined in Sections 1.3 and 1.4. In Cohort 1, exposure to pamiparib will be limited to the first 2 weeks of RT. In Cohorts 2 and 3, pamiparib will be given for the first 4 and 6 weeks of RT, respectively. If 2, 4, or 6 weeks of combination treatment exceeds the MTD, alternative regimens for pamiparib may be explored after discussions with all investigators based on which regimen exceeded the MTD and

what toxicities were observed. For example, if 2 weeks of pamiparib are not tolerated, a schedule of 1 week on, 1 week off, or 1 week on and 3 weeks off may be explored. Depending on data available at that time, a lower dose level of pamiparib may also be explored.

Arm B

The opening of Arm B will depend on the safety of the Arm A combination, and Arm B may be enrolled at the initial dose and schedule of pamiparib found to be safe and tolerable in Arm A. RT will be administered as for Arm A.

The first dose level of TMZ will be lower than or equal to a dose that has been determined to be safe and tolerable in Arm C, and dose escalation will proceed as described for Arm C. The time period of TMZ administration may be the same or shorter than that for pamiparib administration. Similar to Arms A and C, alternative regimens may be explored with adjustments of dose and/or schedule as outlined for Arms A and C.

Arm C

Since TMZ is given as a DNA-damaging sensitizer for pamiparib and to simplify TMZ dosing, flat-dosing will be used for TMZ. The first dose level of 40 mg QD corresponds to 23 mg/m^2 assuming an average body surface area of 1.73 m^2. Subsequent dose levels of 80 mg and 120 mg correspond to 46 mg/m^2 and 69 mg/m^2, respectively. Additional higher dose levels may be explored, and the TMZ dose will not be increased by more than 50% each time. TMZ will be given on Days 1 to 21 of each 28-day cycle based on data and rationale discussed in Sections 1.2, 1.3, and 1.4.

Following the same rationale for pamiparib dosing as for Arms A and B, all patients will receive pamiparib of 60 mg PO BID continuously. If the MTD is exceeded for a combination regimen that is considered inadequate for further exploration based on all data available at that time, alternative regimens may be explored, such as a lower dose of pamiparib, a lower dose of TMZ, and/or alternative dosing schedules for either drug.

Depending on emerging safety data from this and other pamiparib Phase 1 studies, the pamiparib regimen may be switched to QD for one or more of the 3 arms at any time during or after dose escalation. The QD dose of pamiparib may be escalated according to the dose escalation rules in Section 4.2.2 of the protocol.

Once Arm C dose escalation identifies the RP2D for the combination, that combination regimen may be applied in Phase 2 Arm A and B patients (see Section 4.3). Additionally, data emerging from other ongoing studies with pamiparib may be used to determine the combination regimen.

4.2.2. Rules for Dose Escalation

Dose escalation in all 3 arms will occur in accordance with the following modified 3+3 dose escalation rules.

A minimum of 3 patients will be initially enrolled per cohort.

- If none of the first 3 evaluable patients enrolled in a given cohort experience a DLT, dose escalation may proceed.
- If one of the first 3 evaluable patients enrolled in a given cohort experiences a DLT, additional patients (for a minimum of 6 evaluable patients) will be enrolled in that cohort.
    - If less than one-third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than 2 of 6 patients), escalation will proceed to the next higher dose level.

If a DLT is observed in one-third or more of patients (eg, 2 or more of up to 6 patients), the MTD will have been exceeded, and dose escalation will be stopped.

1. Additional patients (for a minimum of 6 evaluable patients) will then be assessed for DLTs at the preceding dose level (if a minimum of 6 evaluable patients had not already been assessed at that dose level).
2. If the MTD is exceeded at a given dose level, a lower or intermediate dose level may be assessed for toxicity in the same manner as described above.

If the MTD is exceeded at a given dose level, the next highest dose level at which less than one-third of evaluable patients in a given cohort experiences a DLT (eg, DLTs in fewer than 2 of 6 patients) will be declared the MTD.

If less than one-third of evaluable patients (eg, DLTs in fewer than 2 of 6 patients) at the highest dose level experience a DLT, this dose level will be declared the MAD.

Available data relevant for dose-escalation decisions for pamiparib (Arm A) or TMZ (Arms B and C), including AEs, laboratory assessments, and PK analyses (as available), will be reviewed by the medical monitor, PK scientist, Safety Scientist and Biostatistician with input from other members of the team as appropriate. On the basis of a review of these data and in consultation with the investigators, a determination will be made as to the next appropriate dose escalation step.

4.2.3. Assessment of Dose-Limiting Toxicity

Dose-limiting toxicities will be assessed during the DLT assessment window starting with the first day of study treatments for all cohorts. The following assessments must be obtained at the end of the DLT assessment window: complete physical examination, vital signs and weight, Eastern Cooperative Oncology Group (ECOG) performance status, ECG, hematology, chemistry, coagulation, urinalysis, AEs, and concomitant medications.

For Arm A, the DLT assessment window will depend on the time period of pamiparib administration during RT and will consist of the time period of combination treatment plus 4 weeks after the last scheduled combination treatment, eg, 6 weeks for Cohort 1 of Arm A when pamiparib is given during the first 2 weeks of RT, and 10 weeks for Cohort 3 of Arm A when pamiparib is given during 6 weeks of RT.

For Arm B, the DLT assessment window will depend on the time period of combined administration of pamiparib and TMZ during RT and will otherwise follow Arm A rules, eg, if TMZ will be given only for the first 3 weeks of pamiparib and RT, then the DLT assessment window will be 7 weeks.

For Arm C, the DLT assessment window will encompass the first cycle of 28 days.

Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for reasons other than a DLT will not be considered evaluable for DLT and will be replaced if needed to meet patient number requirement for dose escalation. Patients who do not experience a DLT and who do not receive ≥ 42 Gy of RT (Arms A and B) and ≥ 70% of scheduled pamiparib (Arms A, B and C) and TMZ (Arms B and C) dosing during the DLT assessment window will not be considered evaluable for DLTs and will be replaced if needed to meet patient number requirement for DLT assessment.

4.2.4. Definition of Dose-Limiting Toxicity

A DLT is defined as one of the following toxicities occurring during the DLT assessment window (as defined for each of the arms and cohorts; Section 4.2.3) and considered by the investigator to be related to pamiparib:

- Grade ≥3 non-hematologic, non-hepatic major organ AE, with the following exceptions:
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤1 with optimal medical management within 3 days
  - Grade 3 electrolyte disturbances that respond to correction within 3 days
- Grade 4 neutropenia lasting > 7 days
- Grade ≥ 3 febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 3 days and requiring transfusion, or any decreased platelet count <15,000/mm^3/ <15.0 x 10^9/L
- Grade ≥ 4 anemia
- Grade ≥ 3 total bilirubin or hepatic transaminases (ALT [SGPT] or AST [SGOT]) with the following exceptions:
  - For patients with Grade 1 hepatic transaminase levels at baseline, a hepatic transaminase level of > 7.5 × upper limit of normal (ULN) will be considered a DLT.

4.3. Details of Cohort-Expansion Stage

Expansion cohorts (up to approximately 60 patients each) may be enrolled at a dose level below or equal to the MTD or MAD of pamiparib (Arm A) or TMZ (Arms B and C) to better characterize the safety and tolerability of pamiparib in combination with RT, RT and TMZ or TMZ alone, and to make a preliminary determination of the efficacy of these combinations.

Arms A and B may have one expansion cohort each, and only patients with unmethylated GBM will be allowed to enroll. After dose escalation in Arm C for GBM patients regardless of *MGMT* methylation status, Arm C may have two expansion cohorts, one for unmethylated GBM and one for methylated GBM.

The rules for continued dosing in the cohort-expansion stage will be identical to those in the dose-escalation stage.

If the frequency of Grade ≥ 3 toxicities or other unacceptable chronic toxicities in the cohort expansion stage of a given arm suggest that the MTD has been exceeded at that dose level, any remaining accrual at that dose level will be halted. Consideration will then be given to enrolling additional patients (up to approximately 60 patients) into an expansion cohort at a lower dose level.

4.4. Duration of Study

The duration of the study from first enrolled patient to final analysis of OS is estimated to be approximately 4 years.

5. STUDY POPULATION

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

For all patients

1. Signed Informed Consent Form (ICF)
2. Age ≥ 18 years
3. Histopathologically confirmed glioblastoma (World Health Organization [WHO] Grade IV) (Louis et al 2016)
    - Tumor must have a supratentorial component.
4. [redacted]
5. Ability to undergo serial MRI scans (computerized tomography [CT] cannot substitute for MRI)
6. Brain MRI scan ≤14 days prior to Day 1
    - Patients requiring glucocorticoids must be on a daily dose equivalent of dexamethasone 4 mg twice daily or less that has been stable for ≥ 7 days prior to the MRI
7. ECOG performance status ≤ 1 (Appendix 3)

8. Ability to swallow whole capsules
9. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 2 weeks prior to Day 1):
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Platelet count ≥ 100 x 10^9/L
   - Hemoglobin ≥ 9 g/dL ≥ 14 days after growth factor support or transfusion if appropriate
   - Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance ≥50 mL/min (calculated using the institutional standard method)
   - Total serum bilirubin ≤ 1.5 x ULN (≤ 4 x ULN, if Gilbert's syndrome)
   - Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 x ULN
   - Albumin ≥ 3 g/dL
   - International Normalized Ratio (INR) ≤ 1.5 and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN
10. Female patients of childbearing potential and female partners of male study patients must agree to practice highly effective methods of birth control (Appendix 4) for the duration of the study, and for ≥ 6 months after last study treatment. In addition, non-sterile male patients must agree to practice highly effective methods of birth control (Appendix 4) and avoid sperm donation for the duration of the study and for ≥ 6 months after the last dose of study drug.
11. Willingness and ability to comply with all protocol-specified requirements

→ **For patients in Arms A and B *(NOT applicable to Arm C)***

12. No previous treatment except surgery (ie, no previous RT, local chemotherapy, or systemic therapy for lower grade central nervous system tumors)
13. Ability to initiate RT ≤ 49 days after surgery, but ≥ 14 days after a biopsy or ≥ 28 days after an open biopsy or a craniotomy with adequate wound healing
14. Documentation of unmethylated *MGMT* promoter status
    - In escalation cohorts, it is preferable to determine *MGMT* status by quantitative methylation-specific polymerase chain reaction (MS-PCR). Other acceptable platforms include pyrosequencing methodologies and methylation sensitive high-resolution melting (MS-HRM) assays with comparable sensitivity, applied to archival or fresh tumor tissue. Sponsor must be notified prior to utilizing alternate assays or if data from acceptable alternate platforms are available.
    - In expansion cohorts, archival or fresh tumor tissue must be submitted for central analysis of *MGMT* status.

→ **For patients in Arm C Escalation *(NOT applicable to Arms A and B)***

15. Documentation of *MGMT* promoter status
    - It is preferable to determine *MGMT* status by MS-PCR. Other acceptable platforms include pyrosequencing methodologies and MS-HRM assays with comparable sensitivity, applied to archival or fresh tumor tissue. Sponsor must be notified prior to utilizing alternate assays or if data from acceptable alternate platforms are available.
16. No prior systemic chemotherapy, other than TMZ, for glioblastoma (including investigational cytotoxic chemotherapy) and no prior anti-angiogenic therapy
    - Prior use of Optune device is allowed with a minimum of 1 week since last Tumor Treating Fields application
17. Histologically confirmed *secondary* glioblastoma will be allowed during the dose escalation phase only
18. Disease that is evaluable or measurable as defined by Response Assessment in Neuro-Oncology (RANO) criteria (Appendix 2)

→ **For patients in Arm C Expansion**

19. Histologically confirmed *de novo* (primary) glioblastoma with unequivocal first progressive disease (PD) after RT with concurrent/adjuvant TMZ chemotherapy as defined by one or more of the following:
    - PD ≥ 3 months after the end of radiotherapy
    - PD that is clearly outside the radiation field
    - PD that has been unequivocally proven by surgery/biopsy
20. Disease that is measurable as defined by RANO criteria (Appendix 2)
    - Patients with recurrent disease must have at least one bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins by MRI scan, with minimal diameters of 10 mm, visible on 2 or more axial slices
21. Documentation of *MGMT* promoter status
    - Tumor tissue (archival or fresh) must be submitted for central analysis of *MGMT* status
    - Patients will be enrolled into 1 of 2 expansion cohorts based on *MGMT* methylation status

5.2. Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

For all patients

1. Chemotherapy, biologic therapy, immunotherapy, or investigational agent ≤ 21 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1
2. Unresolved acute effects of any prior therapy of Grade ≥ 2, except for AEs not constituting a safety risk by investigator judgement
3. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 28 days prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
    - Placement of vascular access device is not considered major surgery.
4. Other diagnosis of malignancy
    - Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, adequately treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed > 2 years ago with no current evidence of disease and no therapy ≤ 2 years prior to Day 1
5. Active infection requiring systemic treatment
6. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection:
    - Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL or patients with active hepatitis C virus (HCV) should be excluded. Note: Inactive hepatitis B surface antigen (HBsAg) carriers, treated and stable hepatitis B (HBV DNA ≤ 500 IU/mL), and cured patients with hepatitis C can be enrolled.
7. Any of the following cardiovascular criteria:
    - Current evidence of cardiac ischemia
    - Current symptomatic pulmonary embolism
    - Acute myocardial infarction ≤ 6 months prior to Day 1
    - Heart failure of New York Heart Association Classification III or IV (see Appendix 5) ≤ 6 months prior to Day 1
    - Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Day 1
    - Cerebral vascular accident (CVA) or transient ischemic attack (TIA) ≤ 6 months prior to Day 1
8. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease or previous gastric resection or lap-band surgery
    - Gastroesophageal reflux disease under treatment with proton-pump inhibitors is allowed (assuming no drug interaction potential)

9. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena ≤ 6 months prior to Day 1
10. Anticoagulation with heparin, warfarin, or other anticoagulants other than the following:
    - Low-dose aspirin and/or non-steroidal anti-inflammatory agents are allowed
    - Use of thrombolytics to establish patency of indwelling venous catheters is allowed
    - Prophylactic anticoagulation for venous access devices is allowed as long as INR is ≤ 1.5 and aPTT ≤ 1.5 × institutional ULN
    - Low molecular weight heparin for treatment of thromboembolic events
11. Use ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1 or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers including known enzyme inducing anti-epileptic drugs (Appendix 6)
12. Pregnancy or nursing
    - Females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1
13. Significant intercurrent illness that may result in the patient's death prior to death from glioblastoma
14. Known history of intolerance to the excipients of the pamiparib capsule

→ **For patients in Arms B and C *(NOT applicable to Arm A)***

15. Known hypersensitivity to any temozolomide component or to dacarbazine (DTIC)
16. Have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

6. STUDY PHASES FROM SCREENING TO END OF STUDY

6.1. Screening

As part of the screening visit, study center personnel will explain to the potential patient all aspects of the study, obtain signed informed consent, and document the informed consent process in the patient's source documents before any study-specific procedures are conducted.

The signed ICF initiates screening that must occur within 28 days of enrollment (Day -28 to Day -1). Study center personnel will access the Interactive Response Technology (IRT) system to obtain a screening identification number for the potential patient, which is generated by IRT.

Required screening assessments, some with shorter screening windows, are listed in Appendix 1. Assessments obtained within 14 days of Day 1 (pregnancy and laboratory assessments: within 7 days

of Day 1) do not have to be repeated on Day 1. Results of standard of-care tests or examinations performed before obtaining informed consent and within the screening windows may be used and do not have to be repeated as long as they meet protocol specifications.

It is highly recommended that general screening assessments such as physical examination and laboratory assessments should be conducted first to rule out ineligibility based on those grounds before more involved and/or invasive procedures are carried out.

The investigator must assess the potential patient for eligibility. Screen failures and consent withdrawals must be documented in the patients' source documents.

6.2. Enrollment

After determination of eligibility, the investigator will complete the treatment authorization form and supporting documentation and provide them to the sponsor and/or designee for review and subsequent approval. No eligibility waivers will be granted.

6.3. Treatment

Day 1 of Cycle 1 is the first day of any study treatment administration (there is no Day 0 in this protocol).

Details on study treatment are provided in Section 7.1.

Study procedures of each clinic visit are outlined in Appendix 1.

On days with PK assessments, study drug should be administered in the clinic in accordance with the schedule for the PK samples. Assessments should be obtained before study drug administration unless stated otherwise in Appendix 1 and should be performed in order of least invasive to most invasive assessment. All safety-related assessments must be reviewed and dose modifications, if necessary, be made by the investigator or subinvestigator before study drug administration.

6.4. Unscheduled Visit

Unscheduled visits may occur any time as necessary as per investigator decision or patient's request for reasons such as additional assessment or follow-up of AEs. If PD is suspected an MRI should be performed

6.5. Permanent Discontinuation of Study Treatment

6.5.1. Reasons for Permanent Discontinuation of Study Treatment

Patients may permanently discontinue study treatment for any of the following reasons:

- Disease progression
- Adverse event(s)
- Death

- Pregnancy
- Major protocol deviations
- Patient withdrew consent for study treatment
    - Patients may voluntarily withdraw consent from study treatment at any time
        - If a patient withdraws consent from the Treatment Phase they should continue with all follow-up visits including survival follow-up
- Start of other anticancer therapy

Other than for treatment completion (Arms A and B), the reason for discontinuation from treatment will be recorded on the electronic case report form (eCRF). Every effort must be made to encourage the patient to complete their EOT visit and appropriate safety follow-ups.

6.5.2. End of Treatment Visit

Patients in Arms A and B who have completed all study treatments per protocol and do not continue on pamiparib in combination with TMZ will have their EOT visit at the end of the Rest Phase, 28 days after RT was completed. Patients continuing on pamiparib in combination with TMZ (maintenance) should follow the schedule of assessments for maintenance treatment (Appendix 1 Table 4).

All other patients with any of the reasons for discontinuation of study treatment listed above will undergo an EOT visit within 7 days after stopping all study treatments.

A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which MRI showed PD may be used as the EOT visit provided that all required assessments were performed. MRI does not have to be repeated if it was performed within 14 days of the EOT visit or at a prior response evaluation that documented PD. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

6.6. Follow-Up Phase

6.6.1. Safety Follow-Up

Approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first, a safety follow-up will occur with the safety assessments outlined in Appendix 1. If new anticancer therapy is inadvertently initiated before this safety follow-up (eg, without the knowledge of the study center team), a safety follow-up should be scheduled as soon as possible.

6.6.2. Efficacy Follow-Up

Patients who were not discontinued from study treatment due to PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed every 8 weeks (±7 days) until

disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 6.7, whichever occurs first.

For efficacy assessments as per protocol, refer to Section 8.3 and Appendix 1. If the patient refuses to return for these visits or is unable to do so, every effort should be made to contact the patient or patient's guardian by telephone to determine the patient's disease status and survival.

6.6.3. Survival Follow-Up

Patients will be followed for survival and further anticancer therapy information post progression via phone contact or other means (with the patient's guardian, if applicable) approximately every 12 weeks as per Appendix 1.

6.6.4. Lost to Follow-Up

If attempts to contact the patient by phone are unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The patient should be contacted by mail in a manner that provides proof of receipt by the patient. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

6.7. End of Study

Premature discontinuation from the study without EOT and any follow-up visits may occur under the following circumstances:

- Patient withdrew consent for study participation
    - Patients may voluntarily withdraw consent from the study at any time.
- Investigator's discretion
- Lost to follow-up
    - The investigator should show due diligence by documenting in the source documents steps taken to contact the patient, eg, dates of telephone calls or registered letters (Section 6.6.4)
- Death
- Study termination by sponsor
- Other, as per the discretion of the sponsor or health authority

7. STUDY TREATMENT

7.1. Study Treatments

7.1.1. Pamiparib

7.1.1.1. Packaging and Labeling

Pamiparib capsules are provided in a container with a child-resistant closure. Patients will receive pamiparib as 20 mg or 60 mg capsules, depending on dose level and availability. The contents of the label will be in accordance with all applicable local regulatory requirements. The label will include at a minimum: drug name, dose strength, contents, sponsor, protocol number, batch number, directions for use, storage conditions, caution statements, retest or expiration date, and space to enter the patient number, visit number, and name of investigator.

7.1.1.2. Handling and Storage

The instructions for drug ordering are in the Pharmacy Binder. The IRT system will also be used for drug supply management. The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug specific requirements.

Pamiparib must be kept at 15°C to 30°C (59°F to 86°F) and protected from light. An accurate study drug accountability log must be maintained and kept up to date at all times.

7.1.1.3. Dosage and Administration

Pamiparib 60 mg will be administered PO BID, once in the morning and once in the evening. The time difference between 2 consecutive doses should be approximately 8 to 12 hours.

Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Patients will be required to fast for at least 1 hour before and 2 hours after each pamiparib administration. Water is allowed during the fasting period.

A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

On days with PK assessments, the morning dose of pamiparib should be administered in the clinic in accordance with the schedule for PK samples (Appendix 1).

7.1.2. Temozolomide

7.1.2.1. Packaging and Labeling

Capsules of TMZ are available in 20 and 100 mg. Please refer to the package insert for detailed information.

7.1.2.2. Handling and Storage

Please refer to the package insert for detailed information.

7.1.2.3. Dosage and Administration

Temozolomide will be administered PO QD, preferably during the same time frame each day (ie always in the morning or always in the evening). The daily dose and schedule will be determined by arm and stage of study as outlined in Section 4.2.1.

On days with PK assessments, TMZ should be administered in the clinic.

Patients will be instructed to swallow the capsules whole, in rapid succession, with water.

A dose of TMZ should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of TMZ should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Antiemetic prophylaxis is usually not required for TMZ. However, prophylaxis with a 5-HT3 antagonist is recommended prior to administration of the first few TMZ doses and should be administered orally 30 to 60 minutes before TMZ treatment. Most patients report optimal nausea control with the use of a 5-HT3 antagonist. If optimal nausea control cannot be achieved, any alternative dosing schedule, such as TMZ administration at night, should be discussed with the medical monitor before implementation.

For patients receiving TMZ (Arms B & C), *Pneumocystis jirovecii* pneumonia prophylaxis is required as outlined in Section 7.2.2.

7.1.2.4. Temozolomide and Pamiparib Drug-drug Interaction Potential

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC (USPI).

CYP phenotyping study using human liver microsomes with selective CYP inhibitors and recombinant CYP enzymes suggests that CYP3A was the major CYP isoform responsible for pamiparib metabolism while CYP2C8 contribute to pamiparib metabolism to a lesser extent. Pamiparib is a moderate inhibitor for CYP2C9 (IC_{50} = 6.48 μM) while its IC_{50} for other CYP

isozymes are all greater than 10 μM. Pamiparib is not a time-dependent CYP inhibitor of the 7 major CYP isozymes tested (please see the Pamiparib IB).

Consequently, the drug-drug interaction potential between pamiparib and TMZ is believed to be low when coadministered.

7.1.3. Radiation Therapy

All patients in Arms A and B will receive RT using either standardized 3-dimensional conformal radiotherapy (3DCRT) technique, intensity modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT) or other 3D conformal technique on a linear accelerator delivering a beam energy of ≥ 6 MV. Radiation therapy, associated 3D radiation therapy planning and stabilization/immobilization procedures will be performed as per local guidelines and taking into account local institutional standard of care.

Patients will receive radiation therapy 5 days per week, in once daily fractions, 1.8 or 2 Gy per fraction, to a total target dose between 58 Gy and 64 Gy in 29 to 33 fractions, for a total duration of up to 7 weeks. The radiation dose should be prescribed to the tumor and its immediate surrounding tissue abnormalities.

Treatment planning should ideally be carried out based on results of the MRI. The target volume should at a minimum encompass the contrast-enhancing lesion (and/or surgical cavity) on T1-weighted post-contrast MRI and an acceptable margin, and may include surrounding tissue abnormalities as demarcated on T2w or FLAIR MR images.

Target Volumes

Recognizing variation in target volume definitions exists, the definition of volumes will be in accordance to recognized standard and local guidelines with appropriate reference to the European Society for Radiotherapy and Oncology (ESTRO)-Advisory Committee on Radiation Oncology Practice (ACROP) guideline for “Target delineation of Glioblastomas” (Niyazi et al, 2016) and the American Society for Radiation Oncology (ASTRO) Evidence-Based Clinical Practice Guideline “Radiation Therapy for Glioblastoma” (Cabrera et al, 2016).

North American radiation oncology cooperative groups generally treat patients in 2 phases, with an initial phase directed at edema (hyperintense region on T2/FLAIR on MRI) in addition to the resection cavity and gross residual tumor (enhancing lesion on T1) followed by a boost directed only at the resection cavity and gross residual tumor. T2 hyperintense regions are targeted in this paradigm because of evidence that T2 hyperintensity sometimes reflects infiltrative and/or low-grade tumor. Some institutions, however, utilize a two-phase treatment paradigm targeting resection cavity and gross tumor alone without specifically targeting edema, citing similar patterns of failure with this approach. (Cabrera et al, 2016). Institutional standards may consist of delivery of a simultaneous integrated boost (SIB) that targets the T2w/FLAIR hyperintense regions and T1w contrast enhancement and resection cavity at the same time.

The European Organization for Research and Treatment of Cancer (EORTC) has adopted a single-phase approach, targeting the enhancing tumor plus cavity with a wide margin throughout the entire treatment, without specifically targeting edema. (Niyazi et al, 2016).

The following are recommendations for target volume definitions.

Gross tumor volume

The gross tumor volume (GTV) is defined by:

- The region of enhancement (without oedema) on post-operative CT/ T1-weighted MRIs (if available) or the region of enhancement (without oedema) on pre-operative CT/T1-weighted MRIs if post op imaging is not available (usually contained in the above),

Plus

- The tumor resection margin (usually contained in the above)

In some tumors no area of enhancement can be seen and the GTV is defined entirely on the T2 abnormality.

For newly diagnosed GBM and in case of complete or subtotal removal, the position of the tumor bed can have shifted, and the GTV should take the new position of the abnormalities on the planning CT scan and any post-operative imaging into account. Post-operative imaging is not mandatory, and it is acceptable to define GTV based on preoperative scans and a planning CT, the latter ideally with IV-contrast.

Clinical target volume

The clinical target volume (CTV) is defined as the GTV plus a margin to account for microscopic spread. This will usually be in the order of 2 to 3 cm but should include all areas of persisting oedema (T2 weighted area on MRI/hypo dense area on CT), but can be reduced in anatomical regions where spread is unlikely (eg, below the tentorium cerebelli) and keeping the volume within the skull.

The CTV extends to the contralateral hemisphere only when midline structures such as the corpus callosum and the contralateral hemisphere are invaded by tumor. The tentorium and meninges should be considered as anatomical borders and therefore a margin of 3-10 mm is sufficient to encompass the microscopic spread at these borders, always keeping the volume within the outer table of the skull.

Planning target volume

The planning target volume (PTV) will provide a margin around the CTV to compensate the uncertainties of the setup and the delivery. This margin should be based upon known individual departmental evaluations. In case it was not investigated the PTV should be defined as CTV plus 3-5 mm margins to all directions. To ensure that surface dose inaccuracies of the treatment planning

system are avoided, the PTV border should be collapsed to inside the natural barriers by limiting to 3 mm from the skin surface.

Additional target volumes and cone downs as and if defined per local standards.

Organs at Risk

To minimize radiation exposure, organ(s) at risk, including eyes, optic nerves, optic chiasm, left and right cochlea, brain stem, and normal brain should be contoured during treatment planning. Every attempt should be made to shield the contoured organs at risk during radiotherapy planning to minimize their dose after satisfying planning requirements for the respective volumes. The maximum administered doses to the organ at risk must be as follows (Scottianti et al, 2015):

Organ at Risk	Maximum Dose (Gy)
Lenses	7
Optic nerves/Optic chiasma	56
Cochlea	≤ 45 (< 34 to contralateral cochlea)
Brainstem	60
Retina	< 45
Lacrimal gland	< 40

The maximal dose to non-specified normal tissues, such as skin and any uninvolved brain hemisphere, is 105% of the prescription dose.

Compliance Criteria

Radiation therapy will be given regardless of the administration of pamiparib (Arm A) and pamiparib in combination with TMZ (Arm B). For example, if administration of pamiparib and/or TMZ has been modified or delayed due to toxicity related to study drugs only, RT may continue.

Interruptions in RT that may be necessitated by skin reaction, brain edema, or other acute reactions are permitted for up to a total of 7 days but the reason for the interruption should be clearly documented in the patient chart and CRF. For interruptions of 8 days or greater, a deviation will be assigned.

For additional details, please see the study Radiation Manual.

7.1.4. Radiation Therapy Adverse Events

Toxicities arising during or after the completion of radiation therapy and attributed to radiation will be assessed according to NCI-CTCAE v4.03 criteria.

7.1.4.1. Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on

the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

7.1.4.2. Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

7.1.4.3. Late Delayed

Possible late delayed effects of radiotherapy, typically occurring >3 months after completion of RT, include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

7.1.5. Dose Holds and Modifications of Study Treatments

7.1.5.1. General Considerations for Modifications of Study Treatments

AEs should be assessed as best as possible regarding their relatedness to one or more study treatment(s). Investigators should discuss potential dose modifications with the medical monitor prior to implementation, if feasible. Regardless of discontinuation of one, two or all study treatment(s), patients should continue on study with regular follow-up as outlined in Section 6.5.2 and Section 6.6.

Patients who experience a DLT during the DLT assessment window, or a clinically significant Grade 2 toxicity or Grade 3 or 4 toxicity considered related to study treatment after the DLT assessment window, may temporarily suspend study treatment. Depending on the toxicity, study treatment may resume within 28 days after discussion with the medical monitor.

Dosing of pamiparib and TMZ can be interrupted for approximately 28 days for medical events that are not associated with toxicity related to these study drugs or disease progression.

Criteria for treatment modifications and suggested guidelines for the management of toxicities related to pamiparib and/or TMZ are summarized below. These general guidelines may be modified at the discretion of the investigator based on best clinical judgement at that time. Any toxicities related to pamiparib and/or TMZ should be managed according to standard medical practice.

Once a dose of pamiparib or TMZ has been reduced, re-escalation is not allowed.

7.1.5.2. Dose Modification Considerations for Combinations with Radiation Therapy

For the patient populations of Arms A and B, RT is an important cornerstone of treatment and should not be compromised because of administration of pamiparib and/or TMZ. Consequently, **RT should only be modified for AEs determined to be solely or mostly related to RT as typically done per standard of care.**

If AEs are encountered that are considered related to pamiparib and/or TMZ, dosing modifications for pamiparib and/or TMZ should be implemented as outlined in Table 3 and Table 4.

If RT is temporarily interrupted for reasons unrelated to pamiparib and TMZ (if applicable), then treatment with pamiparib and TMZ should continue as scheduled. If RT is permanently interrupted for reasons unrelated to pamiparib and TMZ (if applicable), the investigator may consult the medical monitor on the appropriateness of initiating maintenance treatment with pamiparib and TMZ.

7.1.5.3. Dose Modification Guidelines for Temozolomide and Pamiparib

As outlined in Sections 1.2.3, 1.3.1, 1.3.2, and 1.3.4, and discussed in Section 1.5, PARP inhibitors, including pamiparib, show at least partial overlap with the safety profile of TMZ. Therefore, patients in Arms B and C of this study may experience AEs typical for these two drug classes at a higher frequency and/or severity. In addition, patients may encounter AEs that are uniquely caused by the novel combination of pamiparib and TMZ.

As outlined in Section 1.2.3, TMZ is considered a treatment option but not a strongly established standard of care for the patient populations of this study. In the context of this study, the role of TMZ is to sensitize GBM cells to pamiparib through DNA damage that can be caused by relatively low doses of TMZ. Given these considerations, the decision to hold study drugs will always be made for both pamiparib and TMZ combined.

Given the favorable safety profile of pamiparib (Sections 1.3.4 and 1.5), it is reasonable to assume that a Grade 3 or 4 AE is more likely to be due to the addition of TMZ to pamiparib rather than pamiparib on its own. Following this rationale, the decision of a dose reduction will affect TMZ first, and a maximum of 2 TMZ dose reductions will be allowed. Should TMZ dose reduction in itself be insufficient to ensure tolerability of the combination regimen, dose reductions of pamiparib in 20 mg increments may be discussed with the medical monitor, and a maximum of 2 pamiparib dose reductions is allowed. Depending on the toxicity that is triggering a second TMZ dose reduction, the possibility of a concurrent pamiparib dose reduction should be discussed with the medical monitor. A patient must discontinue treatment with pamiparib and TMZ, if, after treatment is resumed at a lower dose, the toxicity recurs with the same or worse severity. Dose levels for TMZ and pamiparib are summarized in Table 3.

Table 3: Individual Dose Levels for Temozolomide and Pamiparib

Dose level	Temozolomide (TMZ)[1]	
	Flat dosing QD	*Dose equivalent*
-1	20 mg	*12 mg/m²*
1	40 mg	*23 mg/m²*
2	80 mg	*46 mg/m²*
3	120 mg	*69 mg/m²*
4	TBD	-

Dose level	Pamiparib[2]	
	BID	*QD*
-2	20 mg	*40 mg*
-1	40 mg	*80 mg*
1	60 mg	*120 mg*

Note: TMZ will be dose-reduced first for a maximum of 2 dose reductions. After discussions with the medical monitor, pamiparib may be dose-reduced next for a maximum of 2 dose reductions. Depending on the toxicity that is triggering a second TMZ dose reduction, the possibility of a concurrent pamiparib dose reduction should be discussed with the medical monitor. Once a dose of pamiparib or TMZ has been reduced, re-escalation is not allowed.
BID = twice daily; QD = once daily; TBD = to be determined

[1] Flat dosing of TMZ is used in this study. Dose equivalent information is provided for reference only and assumes an average body surface area of 1.73 m^2. The starting dose for Arm C is dose level 1. For Arm B, the first dose level of TMZ will be lower than or equal to a dose that has been determined to be safe and tolerable in Arm C.

[2] The dose for pamiparib used in this study is 60 mg BID. A QD schedule may be explored as outlined in Section 4.2.1.

TMZ and pamiparib will be dose-modified as outlined in Table 4. The hold and discontinue guidelines also apply to pamiparib (without TMZ) in Arm A. After a toxicity has adequately resolved, the decision in Arm A of resuming pamiparib treatment at the same dose level versus dose-reducing pamiparib should be made in discussion with the Medial Monitor.

Table 4: Criteria for Modification of Pamiparib and Temozolomide Dosing

Toxicity	Recommended Dose Modification
Hematologic	
Anemia (hemoglobin, Hb)	
Grade 2 (Hb < 10 - 8 g/dL)	First occurrence: continue dosing at current dose level Second and subsequent occurrences: hold pamiparib and TMZ until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ TMZ by 1 dose level and continue pamiparib at same dose
Grade 3 (Hb <8 g/dL)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ TMZ by 1 dose level
Grade 4 (life-threatening consequences; urgent intervention indicated)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline and ↓ TMZ by 1 dose level
Neutropenia (absolute neutrophil count, ANC)	
Grade 3 (ANC <1.0 - 0.5 x 10^9/L)	Hold pamiparib and TMZ until resolved to Grade ≤2 or baseline • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ TMZ by 1 dose level
Grade 4 (ANC <0.5 x 10^9/L)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline and ↓ TMZ by 1 dose level
Febrile neutropenia (ANC <1.0 x 10^9/L with single temperature of >38.3°C or sustained temperature of ≥38°C for >1 hour)	Hold pamiparib and TMZ until resolved and ↓ TMZ by 1 dose level
Thrombocytopenia (platelet count, PLT)	
Grade 3 (PLT <50 - 25 x 10^9/L)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ TMZ by 1 dose level
Grade 4 (PLT <25 x 10^9/L)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline and ↓ TMZ by 1 dose level

Table 4: Criteria for Modification of Pamiparib and Temozolomide Dosing (Continued)

Toxicity	Recommended Dose Modification
Renal	
Serum creatinine	
2-3 x ULN	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ TMZ by 1 dose level
Grade 3 (>3.0 - 6.0 x ULN) and Grade 4 (>6.0 x ULN)	Permanently discontinue pamiparib and TMZ
Hepatic	
Bilirubin	
Grade 2 (>1.5 - 3.0 x ULN) and Grade 3 (>3.0 - 10.0 x ULN)	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline • If resolved ≤7 days, then maintain dose levels • If resolved >7 days, then ↓ TMZ by 1 dose level
Grade 4 (>10.0 x ULN)	Permanently discontinue pamiparib and TMZ NOTE: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (eg review of peripheral blood smear and haptoglobin determination), then ↓ TMZ by 1 dose level and continue treatment at the discretion of the investigator
AST and/or ALT	
Grade 3 (>5 and ≤20 x ULN)	Hold pamiparib and TMZ until AST and/or ALT resolved to ≤5 x ULN or baseline • If ≤5 x ULN within 14 days, then ↓ pamiparib and TMZ by 1 dose level • If second episode, permanently discontinue pamiparib and TMZ • If persistent for >14 days, permanently discontinue pamiparib and TMZ
Grade 4 (>20 x ULN)	Permanently discontinue pamiparib and TMZ

Table 4: Criteria for Modification of Pamiparib and Temozolomide Dosing (Continued)

Toxicity	Recommended Dose Modification
Pancreatic	
Pancreatitis Grade 3 or 4	Permanently discontinue pamiparib and TMZ
Cardiac	
Cardiac - Prolonged QTc interval QTcF >500 msec or >60 msec from the higher of the baseline or predose value	• Obtain triplicate ECGs (5 minutes apart) ~1 hour after initial ECG • If mean QTcF >500 ms or >60 msec from baseline value, hold pamiparib and TMZ until evaluation of ECGs by cardiologist • Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF >500 ms or >60 msec from baseline value confirmed by cardiologist, permanently discontinue pamiparib and TMZ
Cardiac - general Grade 3	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline and ↓ TMZ 1 dose level
Grade 4	Permanently discontinue pamiparib and TMZ
Other adverse events	
Grade 3	Hold pamiparib and TMZ until resolved to Grade ≤1 or baseline and ↓ TMZ by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4	Permanently discontinue pamiparib and TMZ

7.1.6. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient.

The investigator and/or study personnel is responsible for pamiparib accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain pamiparib drug accountability records throughout the course of the study. This person(s) will document the amount of pamiparib received from the sponsor, the amount supplied and/or administered to and returned by patients, if applicable.

7.1.7. Disposal and Destruction

After completion of the study, all unused pamiparib will be inventoried and packaged for return shipment by the hospital unit pharmacist or other designated study personnel. The inventoried supplies will be returned to the sponsor or destroyed on site, after receiving written sponsor approval.

All unused TMZ will be destroyed on site according to regulations and local guidelines.

7.1.8. Treatment of Overdose from Study Drugs

Patients with a suspected overdose should be managed with appropriate supportive therapy as determined by the investigator in consultation with the medical monitor. Any AEs occurring because of an overdose should be reported to the medical monitor as well as being included in standard AE reporting.

7.1.9. Occupational Safety

Pamiparib is not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from the sponsor.

7.2. Concomitant Medications and Non-Drug Therapies

7.2.1. Permitted Medications and Supportive Care

All treatments and supportive care, including glucocorticoids, antiemetic therapy, hematopoietic growth factors and/or red blood cell/platelet transfusions, that the investigator considers necessary for a patient's welfare may be administered at the discretion of the investigator in keeping with the local standards of medical care. All concomitant medications taken during the study will be recorded on the case report form (CRF) including all prescription and over-the-counter (OTC) drugs, herbal supplements, and IV medications and fluids. If changes occur during the study period, documentation of that change in drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last day of study treatment should be recorded.

The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medications.

7.2.2. *Pneumocystis jirovecii* Pneumonia Prophylaxis

Glioblastoma patients receiving concomitant chemoradiotherapy with TMZ 75 mg/m^2 during 6 to 7 weeks or dose-dense TMZ regimens especially in combination with chronic use of corticosteroids have a high risk for developing *Pneumocystis jirovecii* pneumonia (previously known as *Pneumocystis carinii*).

For that reason, all patients in Arms B and C are required to receive *Pneumocystis jirovecii* pneumonia prophylaxis as per the package insert for TMZ. The choice of prophylactic medications will be left to the discretion of the investigator.

7.2.3. Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including surgery, RT (other than protocol-specified), and cytotoxic, biologic, or hormone therapy. Hormone replacement therapy is allowed.

Therapeutic anticoagulation with heparin, warfarin, or other anticoagulants is not allowed, with the exception of low molecular weight heparin for the treatment of patients with thromboembolic events.

Low-dose aspirin, non-steroidal anti-inflammatory agents and thrombolytics to establish patency of indwelling venous catheters are allowed, as is prophylactic anticoagulation for venous access devices as long as INR is ≤1.5 and aPTT ≤1.5 × institutional ULN (Section 5.1).

The primary metabolic pathway for pamiparib involves the CYP3A isoform. The concurrent administration of compounds/substances presented in Appendix 6 are prohibited, as they are associated with possible interactions with pamiparib through the CYP3A metabolic pathway, as well as other various metabolic interactions.

7.2.4. Medications to Be Used with Caution

The primary metabolic pathway for pamiparib involves the CYP3A isoform. Concurrent administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed. Pamiparib is an inhibitor of CYP2C9; careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin. Examples of these medications are listed in Appendix 7, and these should be used cautiously with drug concentration monitoring where appropriate.

In addition to CYP3A, pamiparib can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. See Appendix 7 for medications that should be used with caution for that reason.

8. STUDY ASSESSMENTS

8.1. Study Flow and Visit Schedule

The study-specific assessments and procedures with allowed time windows for Arm A, Arm B, and Arm C, and maintenance treatment for Arms A and B are outlined in Appendix Table 1, Appendix Table 2, Appendix Table 3, and Appendix Table 4, respectively. Assessment of safety of the combination therapies will be based on AE monitoring and reporting (including attribution of AEs and serious adverse events [SAEs]), clinical laboratory testing, vital signs, ECGs, physical examinations, and PK assessments as outlined in Sections 8.2, 8.4, and 8.5, as well as Appendix 1. Assessments of efficacy will occur as outlined in Section 8.3 and Appendix 1.

8.2. Patient Demographics and Other Baseline Characteristics

8.2.1. Demographics

Demographic data will include gender, date of birth (or age), and race/ethnicity.

8.2.2. Medical History

Clinically significant medical history findings (eg, previous diagnoses, diseases or surgeries) started before signing the informed consent, and considered relevant for the patient's study eligibility will be collected and captured, including baseline severity, if ongoing, in the eCRF. Clinically significant is defined as any events, diagnoses or laboratory values that require treatment or follow-up, or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities.

For the GBM history, the date of initial diagnosis and current disease status, staging, sites of disease, prior anticancer therapies, dates administered, responses and duration of response to these treatments will also be recorded.

8.2.3. Other Baseline Characteristics

Information will also be collected regarding prior medications/significant non-drug therapies, childbearing potential (Appendix 4) and any other assessments that are done for the purpose of eligibility for inclusion into the study. For further details on eligibility assessments, please see Section 5 and Appendix 1.

8.3. Tumor Assessments

8.3.1. Magnetic Resonance Imaging (MRI)

Tumor assessments will include all known or suspected disease sites. The minimum recommended MRI sequences include: (i) parameter-matched precontrast and post-contrast inversion recovery-prepared, isotropic 3D T1-weighted gradient-recalled echo; (ii) axial 2D T2-weighted turbo spin-echo acquired after contrast injection and before post-contrast 3D T1-weighted images to control timing of images after contrast administration; (iii) precontrast, axial 2D T2-weighted

fluid-attenuated inversion recovery; and (iv) precontrast, axial 2D, 3-directional diffusion-weighted images. MRIs will be performed at screening (within 14 days of Day 1) and every 8 weeks (±7 days), unless otherwise specified in Appendix 1.

Non-contrast cranial MRI may only be used to document disease in those patients who are allergic to contrast. Tumor assessments should be repeated at the end of treatment visit if more than 4 weeks have passed since the last evaluation.

The same imaging technique used at screening should be used throughout the study.

Anti-tumor activity will be assessed through radiologic tumor assessments conducted at screening, during treatment as specified in the Schedule of Activity, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 4 weeks). All patients' files and radiologic images (in Digital Imaging and Communications in Medicine [DICOM] format) must be available for source verification and for central review.

Assessment of response will be made using the RANO criteria (Appendix 2). Responses should be confirmed with two assessments at least 4 weeks apart. Efficacy evaluations using the RANO criteria involve post-contrast MRI findings, non-contrast T1 and T2 FLAIR images, use of corticosteroid dose, and clinical status per RANO (Ellingson et al 2015).

Following initial evidence of radiographic progressions and due to the potential for pseudo-progression patients may, at the discretion of the investigator, remain on treatment until further imaging is performed 4 to 8 weeks (at the discretion of the investigator) after the initial determination of potential progression.

8.3.2. Central Independent Radiology Facility (IRF)

An IRF may evaluate imaging studies and supportive clinical data in a central and independent fashion. The IRF will comprise board-certified radiologists who will identify baseline lesions and assign post-baseline time point responses. Details regarding IRF member qualification, training, methods, procedures, and other issues relevant to IRF will be described in the IRF Charter.

The IRF will not perform independent clinical evaluations. The IRF may be asked to evaluate response status and may request select clinical data solely to aid in the interpretation of radiographic images. All scans should be sent to the IRF within 1-3 business days of acquisition (as detailed in the Study Manual).

All radiologic studies acquired at all scheduled time points and any additional (unscheduled) radiologic images acquired to evaluate for potential metastatic disease also must be sent to the IRF.

Minimal standards for imaging platform and machine settings as well as information regarding transfer of scan files to the IRF can be found in the Study Imaging Manual.

Assessment of response will be made using the RANO criteria as outlined in Appendix 2.

8.4. Safety

8.4.1. Adverse Events

Safety assessments should be performed at the study center visits throughout the study. See Appendix 1 for the schedule of assessments and windows for assessments.

All AEs and SAEs, regardless of the relationship to study treatment, will be collected per the process and for the time periods outlined in Section 10. The accepted regulatory definition of AEs, SAEs, and important additional requirements for SAE reporting are outlined in Section 10.

8.4.2. Physical Examination, Vital Signs, ECOG Performance Status, Weight and Height

A complete or limited physical examination, vital signs (systolic and diastolic blood pressure, pulse rate and oral, temporal or tympanic temperature), weight, height and ECOG performance status will be performed at time points specified in Appendix 1.

A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, cardiovascular status and neurological status. A limited physical examination should include neurological status and additionally be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

ECOG performance status will be determined as outlined in Appendix 3.

8.4.3. Electrocardiograms

Single 12-lead ECGs with assessment of PR interval, QRS duration, and QTc interval will be obtained as outlined in Appendix 1. Additional ECGs will be performed if clinically indicated. To minimize postural variability, it is important that patients are resting and in a semi-recumbent supine position for ≥ 5 minutes prior to each ECG collection. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimize variability because of the effects of physiologic stress. Screening ECG must be performed within 14 days of Day 1. For the scheduled ECG assessment at the EOT visit, ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

8.4.4. Laboratory Studies

Samples for hematology, chemistry, and coagulation profiles will be drawn and analyzed locally. All other required blood samples will be sent to a central laboratory for analysis throughout the study.

A detailed description of the procedures for sample collection, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the laboratory manual.

Laboratory studies will be performed at the time points specified in Appendix 1 (including allowed windows of assessment) and may also be performed as medically necessary. Laboratory assessments should be done before study treatment. Screening blood and urine tests must be performed within

14 days of Day 1. If they were performed within 7 days of Day 1, they do not need to be repeated on Day 1.

8.4.4.1. Hematology

Hematology includes hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte count.

8.4.4.2. Chemistry

Chemistry includes albumin, alkaline phosphatase, AST, ALT, blood urea nitrogen, chloride, creatinine, glucose, lactic acid dehydrogenase, phosphate, potassium, sodium, total bilirubin, and total protein.

8.4.4.3. Coagulation

The coagulation profile includes INR and aPTT.

8.4.4.4. Urinalysis with Dipstick

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes blood, protein, ketones, glucose, red blood cells, and white blood cells.

8.4.4.5. Hepatitis B Serology Test

Testing for hepatitis B will be performed by the local laboratory at Screening and will include HBV serology (HBsAg, HBsAb and HBcAb) and viral load assessment (HBV DNA).

8.4.4.6. Pregnancy Testing

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include for females with childbearing potential the use of highly effective forms of birth control (Appendix 4) and testing for pregnancy every 28 days. For women of childbearing potential, a screening serum pregnancy test must be obtained within 7 days prior of Day 1. For subsequent pregnancy testing on study and at end of treatment, urine pregnancy tests are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

8.5. Pharmacokinetics

Pharmacokinetic samples will be collected from patients in all cohorts at the following time points (Appendix 1): 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.

8.6. Biomarkers

Patients are required to provide archival tumor tissues for the analysis of candidate predictive biomarkers. This is optional and dependent upon tissue availability in the dose escalation phase but mandatory in the dose expansion phase. Archival tumor tissue, either a formalin-fixed paraffin-embedded block with tumor tissue (preferred) or, ideally, around 15 unstained slides will be sent to the central laboratory for biomarker testing.

Candidate markers will include, but are not limited to:

1. Markers of disease (eg, DNA hypermethylation, PTEN loss or mutational status, EGFR/EGFRviii)
2. Markers related to response or resistance to TMZ (eg, *MGMT* levels and methylation status, APNG, gH2Ax)
3. Markers related to response or resistance to PARP inhibitors (eg, HRD, *BRCA* loss or mutational status, ATM, MRE11, RAD51)

Patients will also provide blood samples to be processed into serum, plasma and cell fractions for the analysis of germline mutations, such as, but not limited to, *BRCA*, and circulating markers, such as, but not limited to, circulating tumor cells (CTCs) and circulating nucleic acids [CNAs].

Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual.

8.7. Appropriateness of Measurements

All safety and PK assessments used in this study are standard, and generally recognized as reliable, accurate, and relevant.

9. DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures (SOPs), working practice documents, and applicable regulations and guidelines. Study center audits may be made periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.1. Data Collection

Data will be entered into the eCRFs in an electronic data capture (EDC) system.

Data collection on the eCRF must follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

9.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file, which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the course of the study, a study monitor will make study center visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 18.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 18.1 or higher.

9.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

10. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

10.1. Adverse Events

10.1.1. Definition and Reporting of an Adverse Event

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE).

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

10.1.2. Assessment of Severity

The investigator will make an assessment of severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE Version 4.03 or higher.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 10.2.

10.1.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study drug will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always provides assessment of causality for every SAE before transmission of the SAE report/eCRF to the sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is at least "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation, *or a causal relationship between the AE and the drug cannot be ruled out*). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

10.1.4. Follow-Up of Adverse Events

When treatment is interrupted or permanently discontinued due to an AE or abnormal laboratory value the patient must be followed at a frequency as medically indicated until resolution or stabilization of the event, whichever comes first.

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of pamiparib or initiation of new anticancer therapy, whichever occurs first. For prolonged hematological toxicities, treatment should be interrupted and blood counts should be monitored weekly until recovery.

If the levels have not recovered to CTCAE Grade ≤ 1 or baseline after 4 weeks, the patient should be referred to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If myelodysplastic syndrome/acute myeloid leukemia is diagnosed, the event should be reported as an SAE regardless of causality.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up or the patient withdraws consent. Once resolved, the appropriate AE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the investigator. The updated SAE report should be resent to the sponsor within the time frames outlined in Section 10.5.1.

10.1.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, hematology, coagulation) or other abnormal assessments (ECGs, X-rays, vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgement of the investigator; in general, these

are the abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, or require close observation, or more frequent follow-up assessments, or further diagnostic investigation.

10.2. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening.

  NOTE: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
  - Hospitalization for social/convenience considerations is not considered an SAE.
  - Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE.
- Results in disability/incapacity.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is considered a significant medical AE by the investigator based on medical judgement (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

10.3. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

10.3.1. Adverse Event Reporting Period

After the ICF has been signed but before study treatment, only SAEs should be reported, as required per Section 10.5.

After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after the last study treatment or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

10.3.2. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

10.4. Specific Instructions for Recording Adverse Events and Serious Adverse Events

10.4.1. Disease Progression

Disease progression and death due to disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an event term. Instead, the symptoms, signs or clinical sequelae that result from disease progression should be reported as the events.

For instance, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as “pleural effusion” instead of disease progression. If a patient experienced a fatal multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the SAE with death as outcome instead of reporting “fatal disease progression” or “death due to disease progression”.

10.4.2. Death

Death is an outcome and not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event, eg “death”, “death of unknown cause”, or “death unexplained”.

10.5. Prompt Reporting of Serious Adverse Events

10.5.1. Timeframes for Submitting Serious Adverse Events

As soon as the investigator determines that the AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form or Pregnancy form

Abbreviations: AE, adverse event; SAE, serious adverse event.

10.5.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 10.5.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality at the time of the initial report as described in Section 10.1.1.

The sponsor will provide contact information for SAE receipt.

10.5.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 10.5.2. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

This protocol is being filed under an Investigational New Drug (IND) protocol amendment with the United States Food and Drug Administration (FDA). Once active, a given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited investigator safety reports are prepared according to the sponsor's policy and are forwarded to investigators as necessary. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow-up report or other safety information (eg, revised IB) from the sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

BeiGene, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions involving the study drug to all regulatory authorities and participating investigators in accordance with International Council for Harmonisation (ICH) Guidelines and/or local regulatory requirements, as applicable. In addition, BeiGene or authorized designee will be responsible for the submission of safety letters to central independent ECs (IECs).

The sponsor (or authorized designee) will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation.

The investigator and IRB/EC will determine whether the informed consent requires revision. The investigator should also comply with the IRB/EC procedures for reporting any other safety information.

Suspected serious adverse reactions and other significant safety issues reported from the investigational product development program will be reported by the sponsor or its designated representative, either as expedited safety reports and/or in aggregate reports—to the relevant, competent health authorities in all concerned countries.

10.6. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study treatment or within 6 months after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

10.7. Poststudy Adverse Events

A poststudy AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period, as defined in Section 10.3.1.

Investigators are not obligated to actively seek AEs or SAEs in former patients. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the SAE related to the study drug, the investigator will notify the sponsor.

10.8. Expedited Reporting to Health Authorities, Ethics Committees and Investigators

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the Pamiparib IB.

11. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All data will be presented by Phase, summarized by arm and cohort in Phase 1b and by arm and expansion cohort in Phase 2. Most of the analysis methods described in this section are directed to the Phase 2 portion of the trial. However, they will be applied to the Phase 1 portion of data analyses whenever appropriate.

Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

11.1. Primary, Secondary and Exploratory Study Endpoints

Please refer to Section 3 for a full listing of study endpoints.

11.2. Statistical Analysis

Hypothesis testing will be performed in Phase 2. In addition, descriptive statistics will be used in describing the antitumor activity and tolerability of the combination regimens in each Phase. CIs will be constructed to describe the precision of the point estimates of interest (eg ORR).

11.2.1. Analysis Set

- The Safety Analysis Set includes all patients who received any study treatment (pamiparib, RT, and/or TMZ). The Safety Analysis Set will be used for all efficacy and safety analyses.
- The Efficacy-evaluable Analysis Set includes patients in the Safety Analysis Set who had baseline and at least one post-baseline tumor assessment, unless discontinued treatment or study early due to clinical progression or death prior to tumor assessment.
- The DLT-evaluable Analysis Set includes patients 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 with sufficient safety assessments. All patients who had a DLT event will be considered DLT-evaluable regardless of study treatment intensity.
- The PK Analysis Set includes all patients for whom valid pamiparib PK parameters can be estimated.

11.2.2. Patient Disposition

The number of patients enrolled, treated and discontinued from study drug, as well as those with major protocol deviations will be counted by arm. The primary reason for study drug discontinuation will be summarized according to the categories in the eCRF. The end-of-study status (alive, dead, withdrew consent, or lost to follow-up) at the data cutoff date will be summarized using the data from the eCRF.

Major protocol deviations will be summarized and listed by each category.

11.2.3. Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by arm in the Safety Analysis Set using descriptive statistics. Continuous variables include age, weight, vital signs, time since initial tumor diagnosis, categorical variables include sex, age group (< 65 vs. ≥ 65 years), race, ECOG performance status, prior therapy for GBM, geographic region, and systemic corticosteroids at baseline.

11.2.4. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary codes. Concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the Clinical Study Report (CSR) for this protocol. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that 1) started before first study treatment and were continuing at the time of first study treatment, or 2) started on or after the date of first study treatment up to 30 days after last study treatment. A listing of prior and concomitant medications will be included in the CSR.

11.2.5. Efficacy Analyses

Tumor assessments by investigators according to RANO will be used to calculate ORR, modified DCR (Arms A and B), DCR (Arm C), PFS, DOR, and CBR, as well as time-point estimate PFS-6m. OS and OS at 6 and 12 months (OS-6m and OS-12m) will be summarized in the efficacy analysis. An optional independent read of the MRI scans may be performed and will be analyzed in the same fashion.

11.2.5.1. Primary Efficacy Analysis

Phase 1b

As described in the protocol objectives, the trial is designed to establish the safety and tolerability of pamiparib in combination with RT and/or TMZ. Evidence of any antitumor activity will be documented and summarized for the Safety Analysis Set as secondary endpoints of the trial.

Phase 2 (Arms A and B)

Modified DCR is the primary efficacy endpoint in Arms A and B. It is defined as the proportion of patients with CR, PR, or SD as the response assessment at the 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).

The null and alternative hypotheses are set as follows:

H_0: Modified DCR = 40%

H_a: Modified DCR > 40%

A binomial exact test will be performed for hypothesis testing in each arm separately in the Safety Analysis Set. If the obtained one-sided p-value is < 0.025, it will be concluded that pamiparib combination therapy showed a statistically significant increase of modified DCR compared to historical control. Therefore, the superiority of pamiparib combination therapy will be demonstrated in this arm.

Two-sided binomial exact 95% confidence interval (CI) of modified DCR will be constructed to assess the precision of the rate estimate.

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

Sensitivity analysis of modified DCR will be carried out in the Efficacy-evaluable Analysis Set.

Phase 2 (Arm C)

ORR is the primary efficacy endpoint in Arm C. 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).

The null and alternative hypotheses are set as follows:

H_0: ORR = 10%

H_a: ORR > 10%

A binomial exact test will be performed within each expansion cohort of Arm C similarly to that described for Arms A and B.

11.2.5.2. Secondary Efficacy Analysis

Descriptive statistics will be used to summarize the secondary efficacy analysis.

DCR is defined as the proportion of patients with best overall response (BOR) of CR, PR, or SD. BOR is defined as the best response recorded from the start of study treatment until data cutoff or start of new anticancer therapy.

CBR is defined as the proportion of patients with BOR of CR, PR, or durable SD (SD ≥24 weeks).

Exact 95% CIs will be calculated for the rate variables: ORR for patients with measurable disease at baseline, DCR, and CBR in the Safety Analysis Set.

PFS is defined as the time from the date of first study treatment to disease progression or death, whichever occurs first.

PFS censoring rule will follow FDA Guidance for Industry, Clinical Trial Endpoints for Approval of Cancer Drugs and Biologics (2007). Patients who have a clinical determination of progression should undergo an MRI, if possible, to correlate radiographic findings with the clinical findings.

Data for patients without disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Data for patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient was known to be progression-free. Data for patients who started new anticancer therapy will be censored at the last tumor assessment date prior to the introduction of new therapy. More details will be given in the SAP.

DOR is defined as the time from the date of the earliest documented response to disease progression or death for any cause, whichever occurs earlier. Only responders will be included in the DOR calculation.

OS is defined as the time from the date of first study treatment to death of any cause.

Time-to-event variables PFS, DOR, and OS will be estimated using the Kaplan-Meier method in the Safety Analysis Set. Kaplan-Meier estimates of PFS, DOR, and OS will be plotted over time. Median PFS, DOR, and OS for each arm will be presented (if possible to estimate), along with their 2-sided 95% CIs using generalized Brookmeyer and Crowley method. The PFS-6m, OS-6m, and OS-12m, defined as the percentages of patients in the analysis population who remain alive and progression-free at 6 months (or alive at 6 or 12 months for OS-6m and OS-12m), will be estimated using Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula. OS will be assessed by 6-month intervals until the last patient enrolled on the study had died.

Selected efficacy endpoints will be summarized in the Efficacy-evaluable Analysis Set as sensitivity analysis.

In Phase 2, modified DCR (in Arms A and B) and ORR (in Arm C) will be summarized in the specified subgroups: sex, age group (< 65 vs. ≥ 65), race, ECOG performance status (0 vs. ≥ 1), prior surgery status, baseline corticosteroid use, mutations, and geographic region. In addition, ORR (in Arm C) will be summarized by relapse status.

11.2.6. Pharmacokinetic Analyses

Population PK analysis may be carried out to include plasma concentrations from this trial in an existing model. PK parameters such as minimum observed plasma concentration (C_{min}) will be summarized, and additional PK parameters such as apparent clearance of the drug from plasma (CL/F) and area under the plasma concentration-time curve from zero to 24 hours post-dose (AUC_{0-24}) may be derived from the population PK analysis if supported by data.

Exposure-response (efficacy or safety endpoints) analysis may be carried out if supported by data. The results of the population PK and exposure-response analyses may be reported separately from the CSR. Details of the PK analyses will be provided in a separate SAP.

11.2.7. Exploratory Analyses

[redacted]

11.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by CTCAE v4.03. Laboratory values, vital signs, physical examinations and ECG findings will also be used in determining the safety of the study treatment.

11.3.1. Extent of Exposure

Extent of exposure to each study treatment will be summarized in each arm descriptively as the number of cycles received (number and percentage of patients) in Arm C, duration of exposure (days), cumulative 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.

The number (percentage) of patients requiring dose reductions, dose holds, and permanent drug discontinuation due to AEs will be summarized by arm. Frequency of dose reductions and study drug withholding will be summarized by categories.

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

11.3.2. Dose-limiting Toxicity

Dose-limiting toxicities in the DLT evaluation period will be summarized descriptively for each dose level in the DLT-evaluable population.

11.3.3. Adverse Events

Adverse Events will be coded using MedDRA Version 18.1 or higher and graded using NCI-CTCAE Version 4.03 or higher. A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date on or after first study treatment or was worsening in severity from baseline (pretreatment) up to 30 days following permanent study treatment discontinuation or initiation of new anticancer therapy, whichever occurs first. All TEAEs will be included in summary tables and in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class (SOC) and preferred term (PT). A patient will be counted only once by the highest grade according to NCI-CTCAE Version 4.03 or higher within an SOC and PT, even if the patient experienced more than one TEAE within a specific SOC and PT. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study treatment. Treatment-related AEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship. Serious AEs, deaths, TEAE of Grade ≥ 3, related

TEAEs and TEAEs that led to study drug/treatment discontinuation, dose reduction or treatment delay will be summarized.

11.3.4. Laboratory Analyses

Clinical laboratory (eg, hematology and chemistry) values will be evaluated as specified in the SAP and collected in the EDC system. Collected values may be a subset of all the values obtained in the requested sampling, eg, a complete blood count with differential may be requested for the evaluation of neutrophils only. Analyzed laboratory values will be flagged and identified as those outside (above or below) the normal range.

Laboratory parameters that are graded in NCI-CTCAE Version 4.03 will be summarized by NCI-CTCAE grade. Shift tables will be provided as appropriate.

11.3.5. Physical Examinations

Physical examination results collected in association with an AE will be listed and summarized.

11.3.6. Vital Signs

Specific vital signs, eg, blood pressure and temperature, will be summarized and listed. The change from baseline will also be presented.

11.3.7. Electrocardiogram

Electrocardiogram assessments will be performed as outlined in Appendix 1. The percentage of patients with abnormal and clinically significant ECG findings will be presented.

11.4. Sample Size Consideration

Approximately 300 patients (60 in Phase 1b and 240 in Phase 2) may be enrolled. The actual sample size in Phase 1b will depend on the number of cohorts enrolled per arm.

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

- Assuming modified DCR of 60% in Arms A and B vs. 40% in historical control, the power of a binomial exact test is 0.874 in each arm when n = 60.
- Assuming ORR of 25% in Arm C vs. 10% in historical control, the power of a binomial exact test is 0.847 when n = 60 per expansion cohort.

With the above assumptions, the binomial exact 95% CI of modified DCR is (46.5%, 72.4%) in Arms A and B and the binomial exact 95% CI of ORR is (14.7%, 37.9%) in each expansion cohort of Arm C.

11.5. Interim Analysis

A brief data summary will be performed once the Phase 1b dose escalation portion is completed. In Phase 2, an interim analysis will be implemented in each arm after approximately the first 20 patients in that arm completed ≥ 2 tumor assessments. This analysis is for futility only. No recruitment stop is planned for this interim analysis. If the conditional or predictive power of demonstrating the final efficacy is < 10%, enrollment in this arm will be halted and safety and efficacy data will be further evaluated before making the decision of whether to stop the arm permanently. Otherwise, the enrollment will be continued to approximately 60 patients in this arm.

11.6. Other Statistical Issues

A final analysis prior to study termination will be performed. The time and scope of the final analysis will be included in the SAP.

Any other statistical/analytical issues will be discussed in the SAP.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Investigator Responsibilities

12.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" ICH guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

Investigators and all subinvestigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify BeiGene or its authorized representative of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol defined activities.

12.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted by the principal investigator and the study center in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The investigator (or sponsor, where applicable) is responsible for ensuring that this protocol, the study center's ICF, and any other information that will be presented to potential patients (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IEC/IRB.

The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study.

Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential patients is amended during the study, the investigator is responsible for ensuring the IEC/IRB reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended

ICF including obtaining IEC/IRB approval of the amended form before new patient consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

12.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the patient can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

During the informed consent process, male patients on Arms B and C should be advised to seek advice on cryoconservation of sperm prior to treatment, because of the possibility of irreversible infertility due to therapy with temozolomide.

12.2.4. Investigator Reporting Requirements

As indicated in Section 10.1, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

12.2.5. Confidentiality

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the US, a study-center specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, eCRFs, the IND, and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study

or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

12.2.6. Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. This also applies to records for those patients who discontinue the study early. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRFs exist within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the use of eCRFs and applications of electronic signatures before the study start and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data on CD-ROMs for archiving the data at the study center.

12.2.7. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene, quantities dispensed to patients, and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the study center's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the study center cannot meet BeiGene's requirements for disposal, arrangements will be made between the study center and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12.2.8. Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

12.2.9. Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

12.3. Sponsor Responsibilities

12.3.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities and the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. As applicable by local requirements, written documentation of regulatory authorities, IRB/IEC and required study center approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and /or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming his/her willingness to remain in the study.

12.3.2. Use of Information and Publication

A CSR will be prepared and provided to the regulatory agency(ies) of participating countries. BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by

the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media *only after the following conditions have been met*:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

12.4. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor.
- Resolve and close all data queries.
- Accountability, reconciliation, and arrangements for unused study drug(s).
- Review of study records for completeness.
- Return of treatment codes to the sponsor.
- Shipment of PK samples to assay laboratories.

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it taking effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory

authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

12.5. Records Retention and Study Files

12.5.1. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archiving at an off-site facility and transfer of ownership of, or responsibility for, the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, arrangements must be made between the investigator and BeiGene to store these in

secure containers outside of the study center so that they can be returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the contract research organization managing the biological samples.

12.5.2. Provision of Study Results and Information to Investigator

When the CSR is completed, the sponsor will provide the major findings of the study to the investigator.

[redacted]

12.6. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.
- Information which is necessary to disclose in order to provide appropriate medical care to a patient.
- Study results that may be published as described in Section 12.3.2.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.7. Joint Investigator/Sponsor Responsibilities

12.7.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.7.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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14. APPENDICES

APPENDIX 1. STUDY ASSESSMENTS

Appendix Table 1: Schedule of Assessments for Arm A (Pamiparib and Radiation Therapy)

Study Phase	**Screening[a]**	**Radiation Therapy (RT)[b]**							**Rest[c]**		**End of Treatment[d]**	**Safety Follow-up[e]**	**Long-Term Follow-up[e]**
Day of Phase	**-28 to -1**	**RT D1**	**RT D8**	**RT D15**	**RT D22**	**RT D29**	**RT D36**	***RT D43***	**Rest D1**	**Rest D15**	**Rest D29**		
Allowed time window			± 2	± 2	± 2	± 2	± 2	*± 2*	+ 3	± 3	+ 3		
Study Day	-28 to -1	1	8	15	22	29	36	*43*	*43-50*	*57-64*	*71-78*	Varies[e]	Varies[e]
Informed consent	X												
Patient enrollment	X[a]												
Demographics and medical history	X												
Complete physical examination[f]	X				X				X		X		
Limited physical examination[f]		X	X	X		X	X	*X*		X			
Vital signs and weight[g]	X	X	X	X	X	X	X	*X*	X	X	X		
Height	X												
ECOG performance status	X	X			X				X		X		
12-lead ECG	X (-14 to -1)	X					X				X		
Hematology[h]	X (-14 to -1)	X	X	X	X	X	X	*X*	X	X	X	X	
Chemistry[i]	X (-14 to -1)	X	X	X	X	X	X		X		X	X	
Coagulation (INR and aPTT)	X (-14 to -1)										X		
Hepatitis B Serology[j]	X (-14 to -1)												
Urinalysis[k]	X (-14 to -1)				X				X		X		
Pregnancy testing[l]	X (-7 to -1)				X				X		X	X	
MRI scan[m]	X (-14 to -1)										X		X (q8w ±7d)
Patient registration	X[a]												
RT[b]		X	X	X	X	X	X	*X*					
Pamiparib[n,d]		X	X	*X*	*X*	*X*	*X*						
Adverse events[o]	X[o]	X	X	X	X	X	X	*X*	X	X	X	X[o]	X[o]

Appendix Table 1: Schedule of Assessments for Arm A (Pamiparib and Radiation Therapy) (Continued)

Study Phase	**Screening[a]**	**Radiation Therapy (RT)[b]**							**Rest[c]**		**End of Treatment[d]**	**Safety Follow-up[e]**	**Long-Term Follow-up[e]**
Day of Phase	**-28 to -1**	**RT D1**	**RT D8**	**RT D15**	**RT D22**	**RT D29**	**RT D36**	***RT D43***	**Rest D1**	**Rest D15**	**Rest D29**		
Concomitant medication(s)[p]	X	X	X	X	X	X	X	*X*	X	X	X	X[p]	X (~q12w)[p]
Pharmacokinetics[q]		X		X									
Blood for biomarkers[r]	X	X		X			X				X		
Tumor tissue[s]	X												
Survival follow-up													X (~q12w)

-7/-14 to -1, Day -7/-14 to Day -1 of screening; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; INR, International Normalized Ratio; MRI, magnetic resonance imaging; q8w ±7d, every 8 weeks ± 7 days; ~q12w, approximately every 12 weeks; RT, radiation therapy

[a] Screening must occur within 28 days of Day 1. Some assessments have a narrower screening window as shown in the table. Assessments obtained within 14 days of Day 1 (pregnancy and laboratory assessments: within 7 days) do not have to be repeated on Day 1. It is highly recommended that general screening assessments such as physical examination and laboratory assessments should be conducted first to rule out ineligibility based on those grounds before more involved and/or invasive procedures are carried out.

[b] RT will be administered once daily (QD) × 5 days/week for 6 to 7 weeks with 1.8 or 2 Gy/fraction for a total target dose of between 58 Gy and 64 Gy. If the time period of RT extends beyond 6 weeks, a clinic visit on Day 43 will be required (gray italics in table).

[c] Day 1 of Rest Phase is defined as the day after RT is completed.

[d] For patients who have completed all study treatment per protocol and who do not continue on maintenance treatment with pamiparib in combination with TMZ, as described further below, the end-of-treatment (EOT) visit will occur at the end of the Rest Phase, 28 days after RT was completed. Patients who discontinued study treatment for any other reason outlined in Section 6.5.1 will undergo the EOT visit within 7 days after stopping all study treatments. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which MRI showed progressive disease (PD) may be used as the EOT visit provided that all required assessments were performed. MRI does not have to be repeated if it was performed within 14 days of the EOT visit or at a prior response evaluation that documented PD. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

After RT is completed, patients will receive no further RT. However, at the discretion of the investigator and after discussion with the medical monitor, patients may continue to receive pamiparib in combination with TMZ until PD, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor, as described in Section 4.1.1 and Section 4.1.2.. This maintenance treatment should begin after the 4-week rest period post-completion of RT (+7 days) to allow for recovery from RT treatment. Patients should follow the Schedule of Assessments for the maintenance treatment (Appendix 1 Table 4).

[e] Safety Follow-up: All patients who discontinue study treatment for reasons other than completion of RT per protocol will have a safety follow-up visit approximately

30 (±7) days after the last day of study treatment to collect AEs and SAEs that may have occurred after the patient discontinued from the study treatment. For patients who have completed all study treatments per protocol, this safety follow-up coincides with the EOT visit.

Long-Term Follow-up: Patients who were not discontinued from study treatment due to PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed every 8 weeks (±7 days) until disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 6.7, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) approximately every 12 weeks.

[f] A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, cardiovascular status and neurological status. A limited physical examination should include neurological status, and additionally be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

[g] Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal or tympanic temperature) will be taken before study treatment and approximately 15 minutes prior to each collection of PK blood samples, if applicable, during the treatment period.

[h] Hematology includes hemoglobin, platelet count, white blood cell (WBC) count, neutrophil count, and lymphocyte count.

[i] Chemistry includes albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), chloride, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and total protein.

[j] Testing will be performed by the local laboratory at Screening and will include HBV serology (HBsAg, HBsAb, and HBcAb) and viral load assessment (HBV DNA).

[k] Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if any assessment on the urine dipstick is abnormal. Urinalysis includes glucose, protein, ketones, blood, red blood cells, and white blood cells.

[l] For women of childbearing potential, a serum pregnancy test must be performed during screening ≤ 7 days prior to Day 1. For subsequent pregnancy testing while on study treatment and at end of treatment, urine pregnancy tests are acceptable. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

[m] Tumors will be assessed at screening by MRI per RANO criteria within 14 days prior to Day 1 and then approximately 4 weeks after completion of RT as part of the EOT visit. Patients without PD at the EOT visit must then be followed with MRIs every 8 weeks (± 7 days) during the Follow-up Phase.

[n] All patients will receive daily pamiparib concurrent with RT starting on Day 1 for a time period that is determined by the Cohort a patient was enrolled into. Patients in Cohort 1 will receive daily pamiparib for the first 2 weeks of RT only (black X), patients in subsequent cohorts will receive pamiparib for longer time periods (gray italics X) as outlined in Section 4. Patients will be required to fast for at least 1 hour before and 2 hours after each pamiparib administration. Water is allowed during the fasting period. A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. On days with PK assessments, pamiparib should be administered in the clinic.

[o] Adverse events and laboratory safety measurements will be recorded at each study visit, graded per NCI-CTCAE Version 4.03 and assessed as outlined in Section 10. After informed consent has been signed but prior to study treatment, only SAEs should be reported. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

[p] Concomitant medications will be recorded at each study visit. All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last day of study treatment should be recorded. The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the

prior and concomitant medications. Concomitant medications include subsequent anticancer therapy information acquired during the Follow-up Phase.

[q] 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. Where pamiparib treatment is administered for only a 2-week (14-day) time period, the 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, processing, and handling of the PK plasma samples will be provided in the laboratory manual.

[r] Blood samples must be collected at screening or on Day 1 (5 mL) for the assessment of germline mutations. Additionally, 3 blood samples (10 mL each) must be collected for the assessment of circulating tumor cells (CTCs) and plasma markers (eg, circulating nucleic acids, CNAs) of GBM, TMZ treatment, and PARP inhibition at screening or on Day 1 before study treatment, and 2 blood samples (10 mL each) must be collected for the assessment of plasma markers (eg, CNAs) on Day 15 and Day 36 before study treatment and at the EOT visit (unless one had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual.

[s] 

Appendix Table 2: Schedule of Assessments for Arm B (Pamiparib, Radiation Therapy and Temozolomide)

Study Phase	**Screening [a]**	**Radiation Therapy (RT)[b]**							**Rest[c]**		**End of Treatment[d]**	**Safety Follow-up[e]**	**Long-Term Follow-up[e]**
Day of Phase	**-28 to -1**	**RT D1**	**RT D8**	**RT D15**	**RT D22**	**RT D29**	**RT D36**	***RT D43***	**Rest D1**	**Rest D15**	**Rest D29**		
Allowed time window			± 2	± 2	± 2	± 2	± 2	*± 2*	+ 3	± 3	+ 3		
Study Day	-28 to -1	1	8	15	22	29	36	*43*	*43-50*	*57-64*	*71-78*	Varies[e]	Varies[e]
Informed consent	X												
Patient enrollment	X[a]												
Demographics and medical history	X												
Complete physical examination[f]	X				X				X		X		
Limited physical examination[f]		X	X	X		X	X	*X*		X			
Vital signs and weight[g]	X	X	X	X	X	X	X	*X*	X	X	X		
Height	X												
ECOG performance status	X	X			X				X		X		
12-lead ECG	X (-14 to -1)	X					X				X		
Hematology[h]	X (-14 to -1)	X	X	X	X	X	X	*X*	X	X	X	X	
Chemistry[i]	X (-14 to -1)	X	X	X	X	X	X		X		X	X	
Coagulation (INR and aPTT)	X (-14 to -1)										X		
Hepatitis B serology[j]	X (-14 to -1)												
Urinalysis[k]	X (-14 to -1)				X				X		X		
Pregnancy testing[l]	X (-7 to -1)				X				X		X	X	
MRI scan[m]	X (-14 to -1)										X		X (q8w ±7d)
Patient registration	X[a]												
RT[b]		X	X	X	X	X	X	*X*					
Pamiparib[n,d]		X	X	*X*	*X*	*X*	*X*						
Temozolomide (TMZ)[o,d]		X	X	*X*	*X*	*X*	*X*						

Appendix Table 2: Schedule of Assessments for Arm B (Pamiparib, Radiation Therapy, and Temozolomide)

Study Phase	**Screening** [a]	**Radiation Therapy (RT)**[b]							**Rest**[c]		**End of Treatment**[d]	**Safety Follow-up**[e]	**Long-Term Follow-up**[e]
Day of Phase	**-28 to -1**	**RT D1**	**RT D8**	**RT D15**	**RT D22**	**RT D29**	**RT D36**	***RT D43***	**Rest D1**	**Rest D15**	**Rest D29**		
Adverse events[p]	X[p]	X	X	X	X	X	X	*X*	X	X	X	X[p]	X[p]
Concomitant medication(s)[q]	X	X	X	X	X	X	X	*X*	X	X	X	X[q]	X (~q12w)[q]
Pharmacokinetics[r]		X		X									
Blood for biomarkers[s]	X	X		X			X				X		
Tumor tissue[t]	X												
Survival follow-up													X (~q12w)

-7/-14 to -1 = Day -7/-14 to Day -1 of screening; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; INR, International Normalized Ratio; MRI, magnetic resonance imaging; q8w ±7d, every 8 weeks ± 7 days; ~q12w, approximately every 12 weeks; RT, radiation therapy

[a] Screening must occur within 28 days of Day 1. Assessments obtained within 14 days of Day 1 (pregnancy and laboratory assessments: within 7 days) do not have to be repeated on Day 1. Some assessments have a narrower screening window as shown in the table. It is highly recommended that general screening assessments such as physical examination and laboratory assessments should be conducted first to rule out ineligibility based on those grounds before more involved and/or invasive procedures are carried out.

[b] RT will be administered once daily (QD) × 5 days/week for 6 to 7 weeks with 1.8 or 2 Gy/fraction for a total target dose of between 58 Gy and 64 Gy. If the time period of RT extends beyond 6 weeks, a clinic visit on Day 43 will be required (gray italics in table).

[c] Day 1 of Rest Phase is defined as the day after RT is completed.

[d] For patients who have completed all study treatment per protocol and do not continue on maintenance treatment with pamiparib in combination with TMZ, the end-of-treatment (EOT) visit will occur at the end of the Rest Phase, 28 days after RT was completed. Patients who discontinued study treatment for any other reason outlined in Section 6.5.1 will undergo the EOT visit within 7 days after stopping all study treatments. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which MRI showed progressive disease (PD) may be used as the EOT visit provided that all required assessments were performed. MRI does not have to be repeated if it was performed within 14 days of the EOT visit or at a prior response evaluation that documented PD. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

After RT is completed, patients will receive no further RT. However, at the discretion of the investigator and after discussion with the medical monitor, patients in the escalation phase may continue to receive pamiparib in combination with TMZ until PD, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor. In the expansion phase, continuation of treatment is mandatory. This maintenance treatment should begin after the 4-week rest period post-completion of RT (+7 days) to allow for recovery from RT treatment. Patients should follow the Schedule of Assessments for the maintenance treatment

(Appendix 1 Table 4).

[e] Safety Follow-Up: All patients who discontinue study treatment for reasons other than completion of RT per protocol will have a safety follow-up visit approximately 30 (±7) days after the last day of study treatment to collect AEs and SAEs that may have occurred after the patient discontinued from the study treatment. For patients who have completed all study treatments per protocol, this safety follow-up coincides with the EOT visit.

Long-Term Follow-up: Patients who were not discontinued from study treatment due to PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed every 8 weeks (±7 days) until disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 6.7, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) approximately every 12 weeks.

[f] A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin, lymph nodes, cardiovascular status and neurological status. A limited physical examination should include neurological status, and additionally be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

[g] Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, and temporal or tympanic temperature) will be taken before study treatment and approximately 15 minutes prior to each collection of PK blood samples, if applicable, during the treatment period.

[h] Hematology includes hemoglobin, platelet count, white blood cell (WBC) count, neutrophil count, and lymphocyte count. Per the Temodar package insert, hematology also needs to be completed on Day 43, which is 21 days after the second dose.

[i] Chemistry includes albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), chloride, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and total protein.

[j] Testing will be performed by the local laboratory at Screening and will include HBV serology (HBsAg, HBsAb, and HBcAb) and viral load assessment (HBV DNA).

[k] Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if any assessment on the urine dipstick is abnormal. Urinalysis includes glucose, protein, ketones, bilirubin, blood, red blood cells, and white blood cells.

[l] For women of childbearing potential, a serum pregnancy test must be performed during screening ≤ 7 days prior to Day 1. For subsequent pregnancy testing while on study treatment and at end of treatment, urine pregnancy tests are acceptable. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

[m] Tumors will be assessed at screening by MRI per RANO criteria within 14 days prior to Day 1 and then approximately 4 weeks after completion of RT as part of the EOT visit. Patients without PD at the EOT visit must then be followed with MRIs every 8 weeks (± 7 days) during the Follow-up Phase.

[n] All patients will receive daily pamiparib concurrent with RT starting on Day 1 for a time period that will be defined following review of the safety data obtained in Arm A, as outlined in Section 4. Patients will be required to fast for at least 1 hour before and 2 hours after each pamiparib administration. Water is allowed during the fasting period. A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. On days with PK assessments, pamiparib should be administered in the clinic.

[o] All patients will receive temozolomide (TMZ) at a dose level as outlined in Section 4.2.1 on the same schedule as pamiparib. Instructions for TMZ administration are the same as for pamiparib. Antiemetic prophylaxis may be provided as described in Section 7.1.2.3. On days with PK assessments, TMZ should be administered in the clinic.

[p] Adverse events and laboratory safety measurements will be recorded at each study visit, graded per NCI-CTCAE Version 4.03 and assessed as outlined in Section 10.

After informed consent has been signed but prior to study treatment, only SAEs should be reported. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

[q] Concomitant medications will be recorded at each study visit. All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last day of study treatment should be recorded. The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medications. Concomitant medications include subsequent anticancer therapy information acquired during the Follow-up Phase.

[r] 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. 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, processing, and handling of the PK plasma samples will be provided in the laboratory manual.

[s] Blood samples must be collected at screening or on Day 1 (5 mL) for the assessment of germline mutations. Additionally, 3 blood samples (10 mL each) must be collected for the assessment of circulating tumor cells (CTCs) and plasma markers (eg, circulating nucleic acids [CNAs]) of GBM, TMZ treatment, and PARP inhibition at screening or on Day 1 before study treatment, and 2 blood samples (10 mL each) must be collected for the assessment of blood markers (eg CNAs) on Day 15 and Day 36 before study treatment and at the EOT visit (unless one had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual.

[t] [redacted]

Appendix Table 3: Schedule of Assessments for Arm C (Pamiparib and Temozolomide)

Study Phase	**Screening[a]**	**Treatment[b]**								**End of Treatment[c]**	**Safety Follow-up[d]**	**Long-Term Follow-up[d]**
Day of Phase	**-28 to -1**	**Cycle 1**				**Cycle 2**		**Cycle ≥3**				
		D1	**D8**	**D15**	**D22**	**D1**	**D15**	**D1**	**D15**			
Allowed time window			± 2	± 2	± 2	+ 2	± 2	± 3	± 3			
Study Day	-28 to -1	1	8	15	22	29	43	57	71	Varies	Varies[d]	Varies[d]
Informed consent	X											
Patient enrollment	X[a]											
Demographics and medical history	X											
Complete physical examination[e]	X					X		X		X		
Limited physical examination[e]		X	X	X	X		X		X			
Vital signs and weight[f]	X	X	X	X	X	X	X	X	X	X		
Height	X											
ECOG performance status	X	X				X		X		X		
12-lead ECG	X (-14 to -1)	X				X		X		X		
Hematology[g]	X (-14 to -1)	X	X	X	X	X	X	X	X	X	X	
Chemistry[h]	X (-14 to -1)	X	X	X	X	X	X	X		X	X	
Coagulation (INR and aPTT)	X (-14 to -1)					X				X		
Hepatitis B serology[i]	X (-14 to -1)											
Urinalysis[j]	X (-14 to -1)					X		X		X		
Pregnancy testing[k]	X (-7 to -1)					X		X		X	X	
MRI scan[l]	X (-14 to -1)							X (q8w ±7d)		X		X (q8w ±7d)
Patient registration	X[a]											
Pamiparib[m]		X	X	X	X	X	X	X	X			
Temozolomide (TMZ)[n]		X	X	X		X	X	X	X			
Adverse events[o]	X[o]	X	X	X	X	X	X	X	X	X	X[o]	X[o]

Appendix Table 3: Schedule of Assessments for Arm C (Pamiparib and Temozolomide) (Continued)

Study Phase	Screening[a]	Treatment[b]								End of Treatment[c]	Safety Follow-up[d]	Long-Term Follow-up[d]
Day of Phase	-28 to -1	Cycle 1				Cycle 2		Cycle ≥3				
		D1	D8	D15	D22	D1	D15	D1	D15			
Concomitant medication(s)[p]	X	X	X	X	X	X	X	X	X	X	X[p]	X (~q12w)[p]
Pharmacokinetics[q]		X		X								
Blood for biomarkers[r]	X	X		X				X		X		
Tumor tissue [s]	X											
Survival follow-up												X (~q12w)

7/-14 to -1, Day -7/-14 to Day -1 of screening; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; INR, International Normalized Ratio; MRI, magnetic resonance imaging; q8w ±7d, every 8 weeks ± 7 days; ~q12w, approximately every 12 weeks

[a] Screening must occur within 28 days of Day 1. Assessments obtained within 14 days of Day 1 (pregnancy and laboratory assessments: within 7 days) do not have to be repeated on Day 1. Some assessments have a narrower screening window as shown in the table. It is highly recommended that general screening assessments such as physical examination and laboratory assessments should be conducted first to rule out ineligibility based on those grounds before more involved and/or invasive procedures are carried out.

[b] Cycle 1 encompasses the dose-limiting toxicity (DLT) assessment window, and assessments of Day 1 of Cycle 2 at the end of the DLT assessment window are required for a patient to be DLT-evaluable. Assessments shown for Cycle 3 apply to all subsequent cycles except for MRI that occurs every second cycle (every 8 weeks).

[c] The end-of-treatment (EOT) visit will occur within 7 days after a patient discontinued study treatment for any of the reasons outlined in Section 6.5.1. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which MRI showed progressive disease (PD) may be used as the EOT visit provided that all required assessments were performed. MRI does not have to be repeated if it was performed within 14 days of the EOT visit or at a prior response evaluation that documented PD. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

[d] Safety Follow-up: all patients who discontinue study treatment will have a safety follow-up visit approximately 30 (±7) days after the last day of study treatment to collect AEs and SAEs that may have occurred after the patient discontinued from the study treatment.

Long-Term Follow-up: Patients who were not discontinued from study treatment due to PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed every 8 weeks (±7 days) until disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 6.7, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) approximately every 12 weeks.

[e] A complete physical examination should include an evaluation of head, eyes, ears, nose and throat, neck, heart, chest (including lungs), abdomen, extremities, skin,

lymph nodes, cardiovascular status and neurological status. A limited physical examination should include neurological status, and additionally be directed at the evaluation of symptoms or specific safety issues. Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

[f] Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal or tympanic temperature) will be taken before study treatment and approximately 15 minutes prior to each collection of PK blood samples, if applicable, during the treatment period.

[g] Hematology includes hemoglobin, platelet count, white blood cell (WBC) count, neutrophil count, and lymphocyte count. For cycle 2 and beyond hematology is only required on Days 1 and 15 however should be measured more frequently based on the patient's blood counts and need for additional monitoring. Per the Temodar prescribing information, hematology also needs to be completed on Day 22 which is 21 days after the first dose.

[h] Chemistry includes albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), chloride, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and total protein.

[i] Testing will be performed by the local laboratory at Screening and will include HBV serology (HBsAg, HBsAb, and HBcAb) and viral load assessment (HBV DNA).

[j] Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if any assessment on the urine dipstick is abnormal. Urinalysis includes glucose, protein, ketones, bilirubin, blood, red blood cells, and white blood cells.

[k] For women of childbearing potential, a serum pregnancy test must be performed during screening ≤ 7 days prior to Day 1. For subsequent pregnancy testing while on study treatment and at end of treatment, urine pregnancy tests are acceptable. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

[l] Tumors will be assessed at screening by MRI per RANO criteria within 14 days prior to Day 1, then every 8 weeks (± 7 days) and as part of the EOT visit. Patients without PD at the EOT visit must then be followed with MRIs every 8 weeks (± 7 days) during the Follow-up Phase.

[m] All patients will receive daily pamiparib as outlined in Section 4. Patients will continue receiving pamiparib in combination with TMZ in Arm C until PD, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor. Patients will be required to fast for at least 1 hour before and 2 hours after each pamiparib administration. Water is allowed during the fasting period. A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. On days with PK assessments, pamiparib should be administered in the clinic.

[n] All patients will receive temozolomide (TMZ) at a dose level as outlined in Section 4. TMZ will be given for Days 1 to 21 of each 28-day cycle. Instructions for TMZ administration are the same as for pamiparib. Antiemetic prophylaxis may be provided as described in Section 7.1.2.3. On days with PK assessments, TMZ should be administered in the clinic.

[o] Adverse events and laboratory safety measurements will be recorded at each study visit, graded per NCI-CTCAE Version 4.03 and assessed as outlined in Section 10. After informed consent has been signed but prior to study treatment, only SAEs should be reported. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

[p] Concomitant medications will be recorded at each study visit. All concomitant medications taken by or administered to the patient within 28 days before Day 1 and 30 days after the last day of study treatment should be recorded. The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medications. Concomitant medications include subsequent anticancer therapy information acquired during the Follow-up Phase.

[q] 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 Cycle 1 Day 1 and Cycle 1 Day 15. If pamiparib treatment is administered for only 2 weeks (14-day) time period, PK sampes will be collected on Day 1 and Day 14 instead. The time of study drug administration on the day prior to Cycle 1 Day 15 (Day 14 if pamipraib is administered for 2 weeks) must be recorded on

the eCRF. Details concerning collection, processing, and handling of the PK plasma samples will be provided in the laboratory manual.

[r] Blood samples must be collected at screening or on Day 1 (5 mL) for the assessment of germline mutations. Additionally, 3 blood samples (10 mL each) must be collected for the assessment of circulating tumor cells (CTCs) and plasma markers (eg, circulating nucleic acids [CNAs]) of GBM, TMZ treatment, and PARP inhibition at screening or on Day 1before study treatment, and 2 blood samples (10 mL each) must be collected for the assessment of plasma markers (eg, CNAs) of GBM on Day 15 and Cycle 3 Day 1 before study treatment and at the EOT visit (unless one had been collected within 14 days). Instructions for the processing, storage, and shipping of samples will be provided in the laboratory manual.

[s] [redacted]

Appendix Table 4: Schedule of Assessments for Maintenance Treatment for Arms A and B (Pamiparib In Combination With Temozolomide)

Study Phase	**Re-Screening[a]**	**Treatment**					**End of treatment (EOT) Visit[b]**	**Safety Follow-up[c]**	**Long-term Follow-up[c]**
Day of Phase	**-7 to -1**	**Cycle 1**		**Cycle 2**		**Cycle ≥3**			
		Day 1	**Day 15**	**Day 1**	**Day 15**	**Day 1**			
Allowed time window			± 3	± 3	± 3	± 3			
Re-Treatment Study Day		1	15	28	43	57	Varies	Varies[c]	Varies[c]
Patient enrollment	X								
Complete physical examination[d]	X	X	X	X	X	X			
Vital signs and weight[e]	X	X	X	X	X	X	X		
ECOG performance status	X	X	X	X	X	X	X		
12-lead ECG	X	X					X		
Hematology[f]	X	X	X	X	X	X	X	X	
Chemistry[g]	X	X	X	X	X	X	X	X	
Urinalysis[h]	X	X					X		
Pregnancy testing[i]	X			X		X	X	X	
MRI scan[j]	X					X (q8w ±7d)	X		X (q8w ±7d)
Pamiparib[k]		X	X	X	X	X			
Temozolomide (TMZ)[l]		X	X	X	X	X			
Adverse events[m]	X	X	X	X	X	X	X	X[m]	X[m]
Concomitant medication(s)[n]	X	X	X	X	X	X	X	X[n]	X (~q12w)[n]
Survival follow-up									X (~q12w)
Tumor tissue[o]							X[o]		

Appendix Table 4: Schedule of Assessments for Maintenance Treatment for Arms A and B (Pamiparib In Combination With Temozolomide) (Continued)

7/-14 to -1, Day -7/-14 to Day -1 of screening; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; D, day; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; INR, International Normalized Ratio; MRI, magnetic resonance imaging; q8w ±7d, every 8 weeks ± 7 days; ~q12w, approximately every 12 weeks

[a] Maintenance treatment should commence following the 4-week rest period post-completion of RT (+7 days) to allow for recovery from RT treatment. A re-screening to confirm continued eligibility must occur within 7 days prior to commencing maintenance treatment. The EOT visit post-completion of the post RT rest period may be considered the re-screening visit provided all assessments were completed. Patients' must continue to meet eligibility criteria prior to commencing maintenance treatment.

[b] The end-of-treatment (EOT) visit will occur within 7 days after a patient discontinued study treatment for any of the reasons outlined in Section 6.5.1. A visit should be scheduled as soon as possible, but the EOT visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. The visit at which MRI showed progressive disease (PD) may be used as the EOT visit provided that all required assessments were performed. MRI does not have to be repeated if it was performed within 14 days of the EOT visit or at a prior response evaluation that documented PD. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

[c] Safety Follow-up: all patients who discontinue study treatment will have a safety follow-up visit approximately 30 (±7) days after the last day of study treatment to collect AEs and SAEs that may have occurred after the patient discontinued from the study treatment.

Long-Term Follow-up: Patients who were not discontinued from study treatment due to PD and meet criteria otherwise (eg, discontinued for AE and no new anticancer therapy) will be followed every 8 weeks (±7 days) until disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 6.7, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) approximately every 12 weeks.

[d] A limited physical examination should include neurological status, and additionally be directed at the evaluation of symptoms or specific safety issues. Changes from the EOT visit of the escalation portion should be recorded. New or worsened abnormalities should be recorded as AEs if appropriate.

[e] Vital signs (systolic and diastolic blood pressure; pulse rate; and oral, temporal, or tympanic temperature) will be taken before study treatment during the treatment period.

[f] Hematology includes hemoglobin, platelet count, white blood cell (WBC) count, neutrophil count, and lymphocyte count. For maintenance cycle 2 and beyond hematology is only required on Days 1 and 15 however should be measured more frequently based on the patient's blood counts and need for additional monitoring. Per the Temodar prescribing information, hematology also needs to be completed on Day 22 which is 21 days after the first dose.

[g] Chemistry includes albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), chloride, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and total protein.

[h] Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if any assessment on the urine dipstick is abnormal. Urinalysis includes glucose, protein, ketones, bilirubin, blood, red blood cells, and white blood cells.

[i] For women of childbearing potential, a serum pregnancy test must be performed during re-screening ≤ 7 days prior to Day 1. For subsequent pregnancy testing while

on study treatment and at end of treatment, urine pregnancy tests are acceptable. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

[j] The scheduling of MRIs during the maintenance phase should continue on an 8 week schedule; ie, the first MRI during maintenance should be completed 8 weeks after the EOT MRI conducted after the rest period following completion of RT. Tumors will be assessed by MRI per RANO criteria every 8 weeks (± 7 days). Patients without PD at the EOT visit must be followed with MRIs every 8 weeks (± 7 days) during the Follow-up Phase. The EOT MRI should only be collected if an MRI has not been performed within 8 weeks or if PD is suspected.

[k] All patients will receive daily pamiparib as outlined in Section 4. Patients will continue receiving pamiparib in combination with TMZ until PD, unacceptable toxicity or death, withdrawal of consent, loss to follow-up, or study termination by sponsor. Patients will be required to fast for at least 1 hour before and 2 hours after each pamiparib administration. Water is allowed during the fasting period. A dose of pamiparib should be skipped if it is not taken within 2 hours of the scheduled time. An extra dose of pamiparib should not be taken to make up for a missed dose. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

[l] All patients will receive temozolomide (TMZ) at a dose level lower than or equal to a dose that has been determined to be safe and tolerable in Arm C of study.

[m] Adverse events and laboratory safety measurements will be recorded at each study visit, graded per NCI-CTCAE Version 4.03 and assessed as outlined in Section 10. After initiation of study treatment, all AEs and SAEs, regardless of relationship to study treatment, will be reported until 30 days after last study treatment or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

[n] Concomitant medications will be recorded at each study visit. All concomitant medications taken by or administered to the patient until 30 days after the last day of study treatment should be recorded. The eCRF entry must include the dose, regimen, route, indication, and start and stop dates of use of the prior and concomitant medications.

[o] If the patient undergoes repeat resection on completion of the maintenance phase, tumor tissue may be collected for the assessment of markers related to GBM, TMZ treatment, and PARP inhibitors.

APPENDIX 2. RESPONSE ASSESSMENT FOR NEURO-ONCOLOGY (RANO) CRITERIA FOR TIME POINT RESPONSES

1. Definitions and Baseline Classification

Baseline is defined as the screening assessment performed immediately prior to commencement of any study treatment.

The following definitions are to be applied:

Measurable Lesions

Measurable lesions are enhancing lesions that can be measured bi-dimensionally with clearly defined margins by computed tomography (CT) or magnetic resonance imaging (MRI).

Minimal Diameter:

Lesions must have two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip.

Note: After baseline, target lesions that become smaller than the minimum requirement for measurement or become no longer amenable to bi-dimensional measurement are to be recorded at the default value of 5 mm for each diameter below 5 mm until the lesion disappears (recorded as 0×0 mm).

Multicentric Lesions

Multicentric lesions are lesions where there is normal intervening brain tissue between the two (or more) lesions. If there is no normal brain tissue between these two (or more) lesions, they will be considered the same lesion.

For multicentric lesions that are discrete foci of enhancement, no more than 3 separately enhancing lesions should be identified and the sum of the product of the diameters (SPD) measured.

Non-Measurable Lesions

All other lesions that do not meet the criteria for measurable disease as defined, as well as all non-enhancing and other truly non-measurable lesions, are considered non-measurable.

A non-measurable lesion will include foci of enhancement that are less than the specified smallest diameter, non-enhancing lesions seen on T2-weighted or fluid attenuated inversion recovery (FLAIR) images, hemorrhagic or predominantly cystic or necrotic lesions, and leptomeningeal tumor. Hemorrhagic lesions often have intrinsic T1-weighted hyperintensity that could be

misinterpreted as enhancing tumor, and for this reason, the pre-contrast T1-weighted image must be examined to exclude baseline or interval sub-acute hemorrhage.

At baseline, lesions are to be identified as follows:

a. ***Target lesions***: Up to 5 measurable lesions, each at least 10 × 10 mm, representative of the patient's disease

b. ***Non-target lesions:*** All other lesions, including all non-measurable lesions and any measurable lesions not chosen as Target lesions

2. Post-Treatment Evaluation

At each evaluation, a time point response is to be determined for target lesions, non-target lesions, and new lesion. The RANO criteria and associated conventions for each post-treatment time point assessment are provided in Appendix Table 5. Overall time point response is derived as described in Appendix Table 6.

Unless progression is observed, overall response can only be determined when all lesions are assessed.

3. Confirmation

Confirmation assessments for overall time point responses of complete response (CR) and partial response (PR) are to be performed no less than 4 but no more than 8 weeks after the initial time point at which a response is seen.

4. Best Response

Best response, incorporating confirmation requirements, will be derived from the series of time point responses and need not be considered when assigning response at each time point.

Appendix Table 5: RANO Criteria For Time Point Responses (TPR)

Prerequisite
If the daily dose of glucocorticoids is not the same for each of the 5 days preceding the current MRI, target or non-target lesion TPR is to be designated NE (not evaluable). To avoid this designation, MRI should be delayed until these glucocorticoid criteria can be met, and every effort should be made to ensure the MRI is performed on schedule while meeting these criteria.

Target Enhancing Lesion (T1/post-contrast) Time Point Response (TPR)

Target Lesion TPR	Criteria
NA	No Target enhancing lesions identified at baseline
PD	≥25% increase in sum of the products of perpendicular diameters (SPD) of the target enhancing lesions compared to the prior MRI (since and including baseline) with the nadir SPD for the target enhancing lesions and on a stable or increasing dose of glucocorticoids. (If the glucocorticoid dose is neither stable nor increased, a Target Lesion TPR of NE is to be assigned.)
NE	≥ 1 target enhancing lesions were not assessed unless progression is observed
CR	Disappearance of all enhancing target lesion(s); and, No glucocorticoids (other than a physiologic replacement dose of a maximum of 1.2 mg dexamethasone equivalent dose per day) taken for the 5 days immediately preceding the date of the current MRI. (If glucocorticoid dose is greater than a physiologic replacement dose, a Target lesion TPR of PR is to be assigned.)
PR	≥50% decrease in the SPD of all target enhancing lesions compared to the baseline MRI; and glucocorticoids stable or decreased, (If the glucocorticoid dose is neither stable nor decreased, a Target Lesion TPR of SD is to be assigned.)
SD	Target lesion TPR not qualify for PD, NE, CR or PR

CR, complete response; MRI, magnetic resonance imaging; NA, not applicable; NE, not evaluable, PD = progressive disease, PR, partial response; SD, stable disease; TPR, time point response.

Appendix Table 5: RANO Criteria For Time Point Responses (TPR) (Continued)

Non-Target Enhancing Lesion (T1/post-contrast) Time Point Response (TPR)

Non-Target Lesion TPR		Criteria
NA		No Non-Target enhancing lesions identified at baseline
PD	MRI: Non-target enhancing (T1/post-contrast)	Unequivocal progression (not due to co-morbid events) of one more non-target enhancing lesions compared to the prior MRI (since and including baseline) with the nadir for the non-target enhancing lesions; and on stable or increasing dose of glucocorticoids. (If the glucocorticoid dose is neither stable nor increased, a Non-Target Lesion TPR of NE is to be assigned.)
NE	≥ 1 non-target enhancing lesions were not assessed unless progression is observed	
CR	MRI: Non-target enhancing (T1/post-contrast)	Disappearance of all enhancing non-target lesion(s); and, No glucocorticoids (other than a physiologic replacement dose of a maximum of 1.2 mg dexamethasone equivalent dose per day) taken for the 5 days immediately preceding the date of the current MRI. (If glucocorticoid dose is greater than a physiologic replacement dose, a Non-Target lesion TPR of PR is to be assigned.)
SD	Non-Target TPR does not qualify for PD, NE, CR or PR	

CR, complete response; MRI, magnetic resonance imaging; NA, not applicable; NE, not evaluable, PD; progressive disease, PR, partial response; SD, stable disease; TPR, time point response.

Time Point Response (TPR) (New Lesions)

New Lesion TPR	Criteria
Yes	1. One or more new lesions (enhancing (T1/post-contrast) or non-enhancing (T1/pre-contrast or T2/FLAIR)) compared to the baseline MRI, regardless of glucocorticoid dose 2. Significant increase on T2/FLAIR (including mass effects) not due to co-morbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects based upon a review of all prior T2/FLAIR images) compared to the T2/FLAIR image at the prior time point (since and including baseline) <u>with the nadir SPD for the target enhancing lesions;</u> and on stable or increasing dose of glucocorticoids steroids. If #2 is met and glucocorticoid dose is neither stable nor increased, a time point response of NE is to be assigned.
NE	Absence of new lesions was not established or T2/FLAIR not assessed.
No	No new lesions compared to baseline MRI and no significant increase onT2/FLAIR (including mass effects)

MRI, magnetic resonance imaging; FLAIR, Fluid-Attenuated Inversion Recovery; NE, not evaluable, TPR, time point response.

Appendix Table 6: Overall Time Point Response

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑
T2/Flair	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[ǂ]
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

CR, Complete Response; FLAIR, Fluid-Attenuated Inversion Recovery; NA, Not Applicable; PD, Progressive Disease; PR, Partial Response; SD, Stable Disease

* Progression occurs when this criterion is present

[ǂ] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration

Reference: Wen PY, Macdonald DR, Reardon DA et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J. Clin. Oncol. 2010;28 (11):1963-72).

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
As published by (Oken et al, 1982). Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

APPENDIX 4. CONTRACEPTION GUIDELINES AND DEFINITION OF CHILDBEARING POTENTIAL

Contraception guidelines

The Clinical Trials Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with the inhibition of ovulation
    - Oral, intravaginal or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
    - Oral, injectable, implantable
- An intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be used in combination with another acceptable method listed above.

Definition of childbearing potential

Childbearing potential is defined as being physiologically capable of becoming pregnant. No childbearing potential is defined as one or both of the following criteria:

- Surgically sterile (bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Post-menopausal, defined as
    - ≥55 years of age with no spontaneous menses for ≥12 months OR
    - <55 years of age with no spontaneous menses for ≥12 months AND with a post-menopausal follicle-stimulating (FSH) concentration >30 IU/mL

APPENDIX 5. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

APPENDIX 6. PROHIBITED MEDICATIONS

Strong and Moderate CYP3A Inhibitors and Strong CYP3A Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease Inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericumperforatum*)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calciumchannel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib
Food products: grapefruit juice (citrus paradisi fruit juice)
Herbal medications: Schisandra sphenanthera
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm from the Indiana University School of Medicine's "Clinically Relevant" Table http://medicine.iupui.edu/flockhart/table htm; from the University of Washington's Drug Interaction Database www.druginteractioninfo.org

APPENDIX 7. MEDICATIONS TO BE USED WITH CAUTION

Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index

- celecoxib[1]
- Phenytoin[2]
- Warfarin[2]

[1] Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when coadministered with a known potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsade de Pointes).

Strong CYP2C8 Inhibitors

- gemfibrozil

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm from the Indiana University School of Medicine's "Clinically Relevant" Table http://medicine.iupui.edu/flockhart/table htm; from the University of Washington's Drug Interaction Database www.druginteractioninfo.org

APPENDIX 8. SIGNATURE OF INVESTIGATOR

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**

PROTOCOL NO: **BGB-290-104**

This protocol is a confidential communication of BeiGene USA, Inc. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene USA, Inc.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene, USA.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

Date: _____

APPENDIX 9. LIST OF COUNTRY-SPECIFIC AMENDMENTS

Amendment 1.1 (UK) – 15 December 2017

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Approval	[redacted] Biomarker/Translation Research 25-Jul-2018 03:03:29 GMT+0000
Approval	[redacted] Regulatory Affairs 25-Jul-2018 03:46:48 GMT+0000
Approval	[redacted] Drug Supply 25-Jul-2018 04:42:57 GMT+0000
Approval	[redacted] Clinical Operations 25-Jul-2018 11:54:05 GMT+0000
Approval	[redacted] Clinical Development 25-Jul-2018 19:31:41 GMT+0000
Approval	[redacted] Clinical Pharmacology 25-Jul-2018 20:51:09 GMT+0000
Approval	[redacted] Biometrics 26-Jul-2018 22:23:47 GMT+0000
Approval	[redacted] Drug Safety 27-Jul-2018 22:20:29 GMT+0000

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Approval	[redacted] Clinical Development 27-Jul-2018 23:17:31 GMT+0000

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