CLINICAL STUDY PROTOCOL

Protocol Title:	**A Phase 1b Study to Assess the Safety, Tolerability, and Clinical Activity of BGB-290 in Combination with Temozolomide (TMZ) in Subjects with Locally Advanced or Metastatic Solid Tumors**
Protocol Number:	BGB-290-103
Original Protocol:	20 March 2017
Version:	1.0
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Version:	3.0
IND No.:	128234
EUDRACT No.:	2017-001553-14
Study Phase:	1b
Sponsor:	BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA

Sponsor Medical Monitor: [redacted]

SIGNATURES

PROTOCOL TITLE: A Phase 1b Study to Assess the Safety, Tolerability, and Clinical Activity of BGB-290 in Combination with Temozolomide (TMZ) in Subjects with Locally Advanced or Metastatic Solid Tumors

PROTOCOL NO: BGB-290-103

BeiGene USA, Inc., Approval:

___ 19 June 2020__
Date

Sponsor Medical Monitor

SYNOPSIS

Name of Sponsor/Company:	**BeiGene USA, Inc.**
Name of Finished Product:	**Pamiparib**
Name of Active Ingredient:	**BGB-290**
Title of Study:	A Phase 1b Study to Assess the Safety, Tolerability, and Clinical Activity of BGB-290 in Combination with Temozolomide (TMZ) in Subjects with Locally Advanced or Metastatic Solid Tumors
Protocol No:	BGB-290-103
Study Centers:	Approximately 35 sites in the United States (US), Europe, Asia, and the Pacific region
Study Phase:	Phase 1b
Treatment Duration:	Patients will receive daily treatment during the study until occurrence of progressive disease, unacceptable toxicity, death, withdrawal of consent, lost to follow-up, or study termination by sponsor.

Objectives:

Primary:

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

Secondary:

- To characterize the pharmacokinetics (PK) of pamiparib and TMZ

Exploratory:

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

Test Product, Dose, and Mode of Administration:	Pamiparib (BGB-290) administered orally (PO) twice a day (BID) in doses of 10 mg, 20 mg, 40 mg, or 60 mg capsules, depending on dose level and availability Temozolomide administered PO once a day (QD) in doses of 5 mg, 20 mg, 100 mg, and 140 mg capsules, depending on dose level and availability
Reference Therapy, Dose, and Mode of Administration:	Not applicable

Study Design:

This is an open-label, multi-center Phase 1b study to evaluate the combined use of pamiparib, a poly (ADP -ribose) polymerase (PARP) inhibitor and TMZ, a DNA-alkylating agent in patients with locally advanced and metastatic solid tumors. This study consists of two phases: a dose escalation phase

and a dose expansion phase. The dose escalation phase of the study will evaluate the safety, tolerability, preliminary efficacy, and PK in addition to determining the MTD or MAD for the combination. In the dose expansion phase of this study, the safety, antitumor activity and PK profile of the combination will be evaluated further. Preliminary biomarkers for efficacy will also be explored through both phases of the study. The dose first phase of the study consists of a modified 3+3 dose escalation scheme utilizing a fixed dose of pamiparib in combination with escalating doses of TMZ. There will be two arms that will undergo dose escalation independently, starting with Dose Level 1. In Arm A, TMZ will be administered once a day during Days 1 to 7 of each 28-day cycle (pulsed). In Arm B, TMZ will be administered once a day continuously during each 28-day cycle. The second phase (dose expansion) of the study will further evaluate the safety and anti-tumor activity of pamiparib in combination with TMZ at the dose and schedule that will be chosen based on all data available from the dose escalation phase. The expansion phase will enroll patients in 6 different cohorts according to indication and/or homologous recombination deficiency (HRD) status as follows: Cohort 1: HRD positive (HRD+) ovarian cancer; Cohort 2: HRD+ triple-negative breast cancer (TNBC); Cohort 3: HRD+ metastatic castration-resistant prostate cancer (mCRPC); Cohort 4: ES-SCLC; Cohort 5: G/GEJ cancer; and Cohort 6: patients who have HRD+ non-squamous non-small cell lung cancer (NSCLC), squamous NSCLC, esophageal cancer, squamous head and neck cancer or soft-tissue sarcomas. Enrollment into these cohorts will occur simultaneously and independently.

It is expected that approximately 250 patients will be enrolled in the entire study. Each expansion cohort will enroll approximately 20-25 patients; cohorts might enroll additional patients based on emerging data, but the total number of patients enrolled in the study will not exceed 250 patients.

Enrollment will start at Dose Level 1 and follow the escalation scheme outlined below (interim dose levels may be tested based on available clinical and PK data).

Dose Escalation

	Arm A (Pulse Dosing of TMZ)		Arm B (Continuous Dosing of TMZ)	
Dose Level	Pamiparib Continuous	TMZ Days 1 to 7, every 28 days	Pamiparib Continuous	TMZ Continuous
-1	60 mg BID	20 mg QD	**60 mg BID**	**20 mg QD***
1	**60 mg BID**	**40 mg QD***	60 mg BID	40 mg QD
2	60 mg BID	80 mg QD	60 mg BID	80 mg QD
3	60 mg BID	120 mg QD	60 mg BID	120 mg QD
≥4	60 mg BID	Increase by ≤ 50% each time until MTD reached	60 mg BID	Increase by ≤ 50% each time until MTD reached

*Starting dose; BID = twice daily; MTD = maximum tolerated dose; QD = once daily; TMZ = temozolomide

The dose and schedule of pamiparib + TMZ intended for the second phase of the study will be determined once the safety and tolerability profiles of each dose escalation and schedule arms has been evaluated. The protocol allows for additional dose adjustments of pamiparib to be explored based on available safety data and the recommendation of the safety team. Patients in the dose expansion phase will be enrolled into one of 6 different cohorts based on their disease characteristics and/or HRD status.

Patients will be evaluated for adverse events (AEs), (all grades, according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 [NCI CTCAE v. 4.03 or higher]), serious AEs (SAEs), and any AEs requiring study drug interruption or discontinuation, from initial dose of study drug until 30 days following their last dose of study drug or until study discontinuation/termination, or until they receive another anticancer therapy, whichever comes first. Patients who, at the time of progression, have an ongoing AE that leads to treatment discontinuation will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different antitumor therapy. If a patient discontinues study drug due to reasons other than disease progression or death, then tumor assessments should continue to be performed following the scheduled assessment plan until disease progression, death, lost to follow-up, or withdrawal of consent to efficacy follow-up.

In the absence of unacceptable toxicities or disease progression, patients will be offered continued study treatment of BGB-290 plus TMZ. Regardless of discontinuation of one or both study drugs, patients should continue on study with regular follow-up. Patients who have discontinued all study drugs should return to the clinic for an end-of-treatment (EOT) visit within 7 days after the last study treatment. After the EOT visit, patients should have regular follow-up for safety, efficacy, and survival.

Planned Number of Patients:	**Dose Escalation Phase:** Approximately 50 patients may be enrolled. More patients may be enrolled if additional doses/schedules are to be evaluated based on emerging data. **Dose Expansion Phase:** Approximately 200 patients in total will be treated in 6 cohorts. Each cohort will enroll approximately 20-25 patients each and will be evaluated separately. Cohorts can be closed due to futility or clinical efficacy based on statistical evaluation or due to insufficient patient recruitment. Cohorts can be also further expanded based on emerging data.

Inclusion Criteria

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

All Cohorts

1. Patient has voluntarily agreed to participate by signing an informed consent.
2. Male or female and ≥ 18 years of age on day of signing an informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
4. Ability to swallow whole capsules
5. Patients who have histologic or cytologic-confirmed malignancy that has progressed to the advanced or metastatic stage.
6. Agree to provide tumor archival tissue
    a. ***Dose Escalation Phase****:* If available, agreement to provide archival tumor tissue for exploratory biomarker analyses
    Note: If archival tumor tissue is not available, an optional fresh biopsy is highly recommended.
    b. ***Dose Expansion Phase***: Patients enrolled in the HRD+ cohorts must provide archival tissue or fresh biopsy (if archival tissue is not available) for prospective central assessment of HRD status. Other cohorts may provide tissue if available for retrospective

analysis

7. Patients must have adequate organ function as indicated by the following screening laboratory values (obtained ≤ 2 weeks prior to Day 1):
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Platelets ≥ 100 x 10^9/L (Note: Criterion must be met without a transfusion within 2 weeks prior to obtaining the sample)
    c. Hemoglobin ≥ 10 g/dL or ≥ 6.2 mmol/L (Note: Criterion must be met without a transfusion within 2 weeks prior to obtaining the sample)
    d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 50 mL/min (calculated using the institutional standard method)
    e. Total serum bilirubin ≤ 1.5 x ULN (total bilirubin must be < 4 x ULN for patients with Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of elevation)
    f. Aspartate and alanine aminotransferase (AST and ALT, respectively) ≤ 3 x ULN OR ≤ 5 x ULN for patients with liver metastases
8. Female patients of childbearing potential and female partners of male study patients must agree to practice highly effective methods of birth control (Appendix 2) for the duration of the study and for ≥ 6 months after the last dose of study drug. In addition, non-sterile male patients must agree to practice highly effective methods of birth control (Appendix 2) and avoid sperm donation for the duration of the study and for ≥ 6 months after the last dose of study drug.
9. Willingness and ability to comply with all protocol-specified requirements

Dose Escalation Phase only

10. Patients must have disease that is either measurable or evaluable per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Dose Expansion Phase only

11. Patients must have measurable disease per RECIST v1.1 criteria (except where noted below).

    Note: Tumor lesions used for freshly acquired biopsies should not be included as target lesions unless there are no other suitable target lesions available.

12. Ovarian Cancer (Expansion Cohort 1)
    a. Patients must have received at least one line of platinum-containing therapy in the advanced or metastatic setting.
    b. Patients must not have progressed or have recurrent disease within 6 months of the completion of the last platinum-containing regimen.
        - Note: Patients can receive additional therapy after the last platinum-containing regimen as long as the criteria for platinum-sensitivity is met.
    c. Patients with known or suspected deleterious mutations in BReast CAncer susceptibility gene *(BRCA)1* or *BRCA2* are classified as HRD+, regardless of the molecular signature result.
        - If HRD or *BRCA1/2* mutation status is unknown or has not been previously evaluated, the patients must undergo tissue screening using the Myriad myChoice® HRD diagnostic test to determine eligibility.

13. Triple-Negative Breast Cancer (Expansion Cohort 2)
    a. Patients with known or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD+, regardless of the molecular signature result.
        - If HRD or *BRCA1/2* mutation status is unknown or has not been previously evaluated, the patient must undergo tissue screening using the Myriad myChoice® HRD diagnostic test to determine eligibility.
    b. 0-1 prior platinum-containing treatment in any treatment setting
        - Note: Patients could have received additional therapy after the last platinum-containing regimen as long as the other eligibility criteria are met.
    c. Received ≤ 3 prior lines of therapy in the advanced or metastatic setting

14. Metastatic Castration-Resistant Prostate Cancer (Expansion Cohort 3)
    a. Patients with known or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD+, regardless of the molecular signature result.
        - If HRD or *BRCA1/2* mutation status is unknown or has not been previously evaluated, the patient must undergo tissue screening using the Myriad myChoice® HRD diagnostic test to determine eligibility.
    b. The patient may be either chemotherapy-naïve or have previously had no more than two taxane-based chemotherapy regimens including docetaxel and carbazitaxel. If docetaxel is used more than once, this will be considered as one regimen.
    c. The patient may be pre-or post-treatment with a novel androgen receptor targeted agent (e.g., abiraterone and/or enzalutamide).
    d. At least 2 weeks since the completion of prior flutamide, bicalutamide, and nilutamide, or enzalutamide and abiraterone treatment
    e. At least 2 weeks from any radiotherapy, with the exception of a single fraction of radiotherapy for the purposes of palliation (confined to one field)
    f. Documented prostate cancer progression as assessed by the investigator with one of the following:
        - Prostate-specific antigen (PSA) progression defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 µg/L (2 ng/ml).
        - Radiographic progression of soft tissue disease by modified RECIST v1.1 criteria
        - Surgically or medically castrated. The testosterone levels do not need to be checked as long as the patient has been on chemical castration or undergone surgical castration for > 4 months. In all cases, the luteinizing hormone-releasing hormone (LHRH) antagonist/agonist is to be continued in these patients.
        - Patients with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration.
15. Extensive Stage Small Cell Lung Cancer (Expansion Cohort 4)
    a. Received ≤ 2 prior lines of therapy
16. Gastric/Gastroesophageal Junction Cancer (Expansion Cohort 5)
    a. Received ≤ 2 prior lines of therapy
17. HRD+ Solid Tumors, Multiple Indications (Expansion Cohort 6)

a. Patient has histologic or cytologic-confirmed advanced (metastatic and/or unresectable)
   - nonsquamous non-small cell lung cancer (NSCLC)
   - squamous NSCLC
   - esophageal cancer
   - squamous head and neck cancer
   - soft-tissue sarcomas (undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, dedifferentiated liposarcoma, myxofibrosarcoma)

b. Patients must have tumors with homologous recombination deficiency (HRD+) as centrally determined by the Myriad myChoice® HRD Plus assay irrespective of any known molecular signature

c. Patients with nonsquamous NSCLC, squamous NSCLC, esophageal cancer and squamous head and neck cancer must have received at least 1 but not more than 3 prior lines of therapy.

d. Patients with soft tissue sarcoma must have received at least 1 but no more than 3 prior lines of therapy. Treatment naïve patients may be allowed if, in the opinion of the investigator, available standard of care first line therapy is not appropriate.

Exclusion Criteria

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

1. Known hypersensitivity to any temozolomide component or to dacarbazine (DTIC)
2. Prior treatment with a PARP inhibitor
3. Received chemotherapy, biologic therapy, immunotherapy, or investigational agent within 3 weeks prior to Day 1 (or ≤ 5 half-lives, whichever is shorter) (unless otherwise noted in the Inclusion Criteria)
4. Patients who are considered to be refractory to platinum-based therapy (e.g., progressive disease at the first tumor assessment while receiving platinum treatment) (for patients in Dose Expansion Phase only)
5. Have any unresolved acute effects of any prior therapy of Grade 2 or higher, except for AEs not constituting a safety risk by investigator judgment
6. Had a major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
   - Placement of a vascular access device is not considered major surgery
7. Have 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.
8. Patient who has received local radiotherapy of non-target lesions for local symptom control within the last 4 weeks must have recovered from any adverse effects of radiotherapy before recording baseline symptoms.
9. Have untreated leptomeningeal or brain metastasis. Patient with previously treated brain metastases is eligible if the metastases have shown no progression on brain computed

tomography (CT) or magnetic resonance imaging (MRI) over at least 4 weeks, the patient has no symptoms due to the brain metastases, and the patient has been off corticosteroids for ≥ 2 weeks.

10. Have active infection requiring systemic treatment
11. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection as follows:
    - Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL should be excluded. Note: Inactive HBsAg carriers and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL) can be enrolled. Patients receiving antivirals at screening should have been treated for > 2 weeks before the first dose of study drug(s).
12. Have 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 (Appendix 3) ≤ 6 months prior to Day 1
    - Grade ≥2 ventricular arrhythmia ≤ 6 months prior to Day 1
    - Cerebral vascular accident (CVA) ≤ 6 months prior to Day 1
13. Have an active inflammatory gastrointestinal disease, chronic diarrhea, or had previous complete gastric resection or lapband surgery
    Note: Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed (assuming no drug interaction potential).
14. Use or have anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers ≤10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1 (Protocol Appendix 4)
15. Are pregnant or nursing (females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1)
16. Have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

Study Endpoints:

Primary Endpoints

Escalation: Incidence and nature of DLTs

Expansion: Incidence, nature, and severity of AEs, graded according to the NCI CTCAE v. 4.03
Objective response rate (ORR), as assessed using RECIST v1.1

Secondary Endpoints

Pharmacokinetic parameters of pamiparib and TMZ, including but not limited to C_{trough}

Time-to event- endpoints: e.g., duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survivals (OS)

Exploratory Endpoints

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

Statistical Methods:

Approximately 50 patients will be enrolled in the dose escalation phase. A sample size of 20-25 patients in an expansion cohort will provide the half width of the 90% confidence interval of the ORR

approximately 13% to 20% when the observed ORR is approximately 40%. Hence, the low bound is above 20%. This is considered adequate in the preliminary assessment of anticancer activity of pamiparib and TMZ combination therapy. An expansion cohort can be further expanded to confirm efficacy. Up to 200 patients will be enrolled in the expansion cohorts.

Populations:

Safety Population includes all patients who received any dose of pamiparib and/or TMZ. The Safety Population will be used for all safety analyses.

Efficacy Evaluable Population includes patients in the Safety Population who had measurable disease at baseline (or prostate cancer patients as per inclusion criteria 14f) and had at least one post-baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

DLT Evaluable Population includes patients who received ≥ 70% of each study drug during the DLT assessment window and had sufficient safety evaluation. Additionally, patients who had a DLT event during the DLT assessment window despite receiving < 70% of the scheduled dose will also be considered evaluable.

PK Population includes all patients for whom valid pamiparib PK parameters can be estimated.

Safety Analysis:

Safety will be assessed by monitoring and recording of all AEs graded by the NCI CTCAE v. 4.03. Laboratory values (CBC, clinical chemistry, coagulation, and urinalysis), vital, physical exams, and ECG findings will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety Population.

DLT Analysis:

Dose-limiting toxicity in the DLT evaluation period will be used to determine the dose and schedule of pamiparib plus TMZ in the expansion cohorts. The DLT events will be summarized descriptively at each combination dosing level in the DLT Evaluable Population.

Pharmacokinetic Analyses:

Population PK analysis may be carried out for pamiparib to include plasma concentrations from this study in an existing model. PK parameters such as C_{min} will be summarized and additional PK parameters, such as apparent clearance (CL/F) of the drug from plasma and area under the plasma concentration-time curve (AUC) may be derived from the population PK analysis if supported by data. Population PK analysis may be reported separately from the final clinical study report (CSR).

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

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

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Abbreviation	Definition
AE	adverse event
ADL	activities of daily living
AIC	5-amino-imidazole-4-carboxamide
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
ATM	ataxia-telangiectasia mutated
AUC	area under the plasma concentration-time curve
BER	base excision repair
BID	twice daily
BGB-290	study drug code
BOR	best overall response
BRCA	BReast CAncer susceptibility gene
gBRCAm	germline BReast CAncer susceptibility gene mutation
BSA	body surface area
BUN	blood urea nitrogen
CA-125	carcinoma antigen-125
CBC	complete blood count
CHO	Chinese hamster ovary
CI	confidence interval
CL/F	apparent clearance
C_{min}	minimum observed plasma concentration
C_{max}	maximum observed plasma concentration
C_{trough}	lowest concentration reached before the next dose administered
CNA	circulating nucleic acids
CNS	central nervous system
CNA	circulating nucleic acids
CR	complete response

Abbreviation	Definition
CSR	clinical study report
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
CVA	cerebral vascular accident
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DSB	double strand break
DTIC	dacarbazine
EC_{50}	half maximal effective concentration
eCCGs	eCRF Completion Guidelines
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EOT	end-of-treatment
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FP	fluorescence polarization
GCIG	Gynecologic Cancer Intergroup
GCP	Good Clinical Practice
G/GEJ	gastric/gastroesophageal junction
GLP	Good Laboratory Practices
*g*BRCA	germline BRCA
HCT	hematocrit
hERG	human ether-a-go-go related gene
HRD	homologous recombination deficiency

Abbreviation	Definition
HR	hazard ratio
HRR	homologous recombination repair
Hgb	hemoglobin
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half inhibitory concentration
IEC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
KM	Kaplan-Meier
LDH	lactic acid dehydrogenase
LHRH	luteinizing hormone-releasing hormone
MAD	maximum administered dose
mCRPC	metastatic castration-resistant prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MPG	N-methylpurine glycosylase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MTIC	5-(3-methyltriazen-1-yl)imidazole-4-carboxamide
NAD	nicotinamide adenine dinucleotide
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
Pamiparib	BGB-290
PAR	poly(ADP-ribose)
PARP	poly(ADP-ribose) polymerase
PBMCs	peripheral blood mononuclear cells
PCWG2	Prostate Cancer Clinical Trials Working Group 2

Abbreviation	Definition
PD	pharmacodynamic
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PLT	platelet
PO	orally
PR	partial response
PSA	prostate-specific antigen
PT	preferred term
QD	once daily
QTc	QT interval corrected for heart rate
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCLC	small cell lung cancer
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SSB	single strand DNA breaks
$t_{1/2}$	elimination half-life
T_{max}	time to reach maximum (peak) plasma concentration
TEAE	treatment-emergent adverse event
TMZ	temozolomide
TNBC	triple-negative breast cancer
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Poly (ADP-ribose) Polymerase Inhibitors 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 (SSBs) into double strand- breaks (DSBs) during DNA replication. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP-ribose) (PAR) into 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. [1]

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 normal cells, PARP trapping is overcome by homologous recombination repair (HRR) factors such as BReast CAncer susceptibility gene (*BRCA*)*1*/*2*, ataxia-telangiectasia mutated (ATM), and other HRR proteins. Thus, cancer cells with homologous recombination deficiencies (HRDs) are more susceptible to PARP inhibitors in a mechanism known as synthetic lethality, which is when two conditions in combination are lethal but independently would not cause cell death. [2]

In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained anti-tumor responses as a single agent in patients with *BRCA1*- or *BRCA2*-mutant tumors, while achieving a favorable safety profile. Olaparib and rucaparib are approved as single agent for patients with advanced ovarian cancer who have germline mutations in the BRCA gene. (Approved product package inserts are available online).

Pamiparib (also known as BGB-290) is a potent and selective inhibitor of PARP1 and PARP2. Pamiparib showed potent ability to trap PARP proteins on damaged DNA (DNA-trapping activity) and anti-proliferative activity against a number of cell lines harboring BRCA gene mutations or homologous recombination defects.

1.2. PARP Inhibitors in the Treatment of Solid Tumors

As discussed above PARP inhibitors induce synthetic lethality in cancers with HRD. This study will enroll patients with tumors likely to harbor DNA damage repair deficiencies susceptible to treatment with PARP inhibitors as described below.

Breast Cancer

Breast cancer is a clinically and biologically heterogenous disease characterized by diverse genomic signatures and protein expression patterns. Up to 10% of breast cancers can be linked to germline mutations in *BRCA1* and/or *BRCA2* genes. [3] Both *BRCA1* and *4* are tumor suppressor genes; and when mutated, can lead to a higher risk of cancer by disabling DNA repair processes called homologous recombination or homology directed repair. [4, 5]. Many investigations have shown that HRD is critical for the response to both platinum and PARP inhibitor therapy.

Triple-negative breast cancer (TNBC) is considered an aggressive disease, characterized by high tumor grade, absence of both hormone receptors (estrogen and progesterone) and the HER2 receptor and frequent association with *BRCA1* mutations.

Clinical studies support the use of platinum compounds in *BRCA1/2* mutated breast cancer in the neo-adjuvant and advanced disease treatment setting including metastatic TNBC. [6, 7, 8, 9] The TNT study [9] demonstrated no difference in overall tumor response rates or progression-free survival (PFS) with carboplatin treatment compared to docetaxel for an unselected population of patients with TNBC. However, carboplatin was associated with improved objective response rate (ORR) and PFS in the subgroup of patients with germline *BRCA1/2* mutated breast cancer. When added to either docetaxel [10] or gemcitabine, [11] clinical outcomes were superior in the combination treatment arms containing cisplatin over the comparator monotherapy arms.

It has been hypothesized that inhibition of PARP, in combination with DNA-damaging chemotherapeutics, would be highly effective in tumors lacking BRCA function. [12, 13, 14, 15]

PARP inhibitors have been tested clinically in breast cancer patients with *BRCA1/2.* In a single-arm, open label study, olaparib (400 mg or 100 mg orally twice daily [BID]) was administered to women with *BRCA1*- and/or *BRCA2*-mutant, advanced breast cancer (of which > 50% were triple negative). [16] Patients in the 400 mg BID treatment group had an ORR of 41% and PFS of 5.7 months. The most commonly reported grade 3 adverse events (AEs) were fatigue, nausea, and vomiting.

Other Phase 3 studies investigating single-agent PARP inhibitors in patients with germline *BRCA1/2* mutated breast cancer are ongoing (olaparib, niraparib, and talazoparib).

Ovarian Cancer

Currently two PARP inhibitors, olaparib and rucaparib, have been Food and Drug Administration (FDA) approved for women with advanced ovarian cancer with *BRCA1/2* mutation. In addition, olaparib was approved by the European Medicines Agency (EMA) as maintenance therapy for ovarian cancer patients with *BRCA1/2* mutation.

Data from clinical studies support the use of PARP inhibitors for women with platinum-sensitive epithelial ovarian cancer (EOC). [17, 18, 19] In a randomized study with ~300 women with platinum-sensitive high-grade recurrent EOC, patients were randomly assigned to treatment with the PARP inhibitor olaparib or placebo. [20] Results from this study showed a significant improvement in PFS in patients treated with olaparib compared with placebo (8 versus 5 months; hazard ratio [HR] for progression or death 0.35, 95% confidence interval (CI) 0.25-0.49), although interim analysis found no overall survival (OS) benefit (30 months in both; HR 0.94; 95% CI; 0.63-1.39). A subanalysis of data from this study showed a significant benefit in PFS with olaparib compared with placebo among patients with a known BRCA mutation (median, 11 versus 4 months; HR 0.18; 95% CI; 0.10-0.31), with a trend towards improved OS (HR 0.73; 95% CI; 0.45-1.17), which became more pronounced at a longer follow-up (>5 years). [17, 18]

In a recent double-blind Phase 3 study (NOVA), 553 patients with platinum-sensitive, recurrent ovarian cancer were randomized 2:1 to receive a PARP inhibitor niraparib or placebo. [19] Patients were stratified according to presence or absence of a germline *BRCA* mutation (*gBRCA*). The non-*gBRCA* cohort was further classified by HRD status and also included patients with somatic *BRCA* mutations. Patients treated with niraparib had an increased PFS in all cohorts compared with placebo. In the *gBRCA* group, PFS was 21.0 versus 5.5 months (HR 0.27; 95% CI; 0.17-0.41). In the overall non-g*BRCA* cohort, PFS was 9.3 versus 3.9 months (HR 0.45; 95% CI; 0.34-0.61). In the HRD positive (HRD+) subgroup of the non-g*BRCA* cohort, PFS was 12.9 versus 3.8 months (HR 0.38; 95% CI 0.24-0.59). The most common grade 3 or 4 toxicities

associated with niraparib were thrombocytopenia (34%), anemia (25%), and neutropenia (20%). Myelodyspastic syndrome (MDS) occurred in 5 of 367 patients (1.4%) who received niraparib.

Another PARP inhibitor, veliparib, was evaluated in a Phase 2 study in 50 women with a known *BRCA* mutation. Veliparib treatment resulted in a 26% ORR and the median PFS and OS were 8 and 20 months, respectively. [21]

Prostate Cancer

Prostate cancer is the second most common cancer in men worldwide. [22] Recent sequencing data indicates that more than 20% of metastatic castration-resistant prostate cancer (mCRPC) have HRD due to germline and/or somatic loss-of-function in key homologous recombinant genes including *BRCA2, ATM, CHEK2, NSBP1, FANCJ*, that could potentially confer a 'BRCAness' phenotype and susceptibility to PARP inhibition via synthetic lethality. [23, 24, 25, 26] Recently, it has been shown that prostate cancer patients with germline *BRCA1/2* mutations have a higher risk of nodal or distant metastases and poorer overall survival than patients without mutations. [27] Data from clinical studies has demonstrated that these patients respond to treatment with PARP inhibitors. [28]

In a Phase 2 study, 49 patients with mCRPC who had received at least two prior regimens and had received prior docetaxel chemotherapy were treated with the PARP inhibitor olaparib (400 mg BID). [24] In this study, 16 patients (33%), had DNA repair mutations. The primary endpoint of the study was a composite response rate that included ORR, a ≥ 50% decrease in serum prostate-specific antigen (PSA), and/or a decrease in circulating tumor cells. Fourteen of the 16 (88%) patients with DNA repair mutations had a response based upon these criteria compared to only 1 of 33 (3%) patients without an identified DNA-repair gene abnormality.

In another Phase 2 study, 153 patients with mCRPC were treated with abiraterone plus prednisone or abiraterone, prednisone, and veliparib. [29] There was a trend toward improvement in the PSA response rate (71 versus 64%) and in PFS (11.0 versus 8.8 months) with the addition of veliparib, but neither were statistically significant. However, there were statistically significant differences in the PSA response rate (89 versus 57%) and measurable disease response rate (80 versus 38%) in patients with an identifiable defect in a DNA repair gene.

Gastric Cancer

Genetic abnormalities in gastric cancer include alterations in the DNA damage response gene *ATM*. The loss of *ATM* has been demonstrated to be synthetically lethal with inhibition of PARP, supporting the use of platinum-based treatment as well as PARP inhibitors.

Studies showed that gastric cancer cell lines, particularly those with a low expression level of ATM protein, are sensitive to olaparib. [30, 31] A randomized, double-blind placebo-controlled Phase 2 study was conducted in 124 patients with recurrent or metastatic gastric cancer treated with olaparib (100 mg BID daily) in combination with paclitaxel (80 mg/m^2 on days 1, 8, and 15 of every 28-day cycle) or placebo. [32] Results from this study showed the combination therapy significantly improved OS in both the overall population (median 13.1 versus 8.3 months) and in

those whose tumors contained low levels of ATM protein. However, there was no difference in PFS in either the overall population or in those patients with ATM-low tumors.

A Phase 3 clinical study with paclitaxel with or without olaparib as a second line treatment recently reported results. [33] Asian patients with advanced, previously treated gastric cancer were treated with either paclitaxel or paclitaxel in combination with the PARP inhibitor olaparib; 18% of 535 randomized patients were ATM-deficient. Results of the study in the overall population demonstrated numerically higher overall survival for patients treated with olaparib plus paclitaxel (6.9 versus 8.8 months; HR 0.79; p =0.0262). However due to a statistical correction made due to inclusion of a co-primary endpoint of the ATM-deficient subgroup, this did not reach statistical significance (which would have required a p value of < 0.025). In the ATM-deficient subgroup, radiological response rates were significantly higher for patients treated with olaparib (37% versus 16%; p=0.03), and a non-statistically significant trend towards improvement in overall survival was also noted (10 versus 12 months; HR 0.73; p = 0.25). [34]

Small Cell Lung Cancer

Small cell lung cancer (SCLC) constitutes about 15% of newly diagnosed lung cancer cases and occurs predominantly in cigarette smokers. [35] Approximately 50% of SCLC patients have brain metastases at the time of postmortem examination.

Preliminary data from Phase 1 studies has demonstrated some efficacy of PARP inhibitors in SCLC patients. In a Phase 1 study, talazoparib was administered as a single agent in patients with previously treated, advanced SCLC with germline mutations in *BRCA1* and *BRCA2*. [36] In this study, 10% of patients treated with talazoparib had a partial response and 25% had a clinical benefit (complete response [CR], partial response [PR], or stable disease [SD] lasting ≥ 16 weeks) with a median duration or response of 13.7 weeks (95% CI; 12.0-15.3 weeks). The most common adverse events in this study were myelosuppression, fatigue, nausea, and alopecia.

A Phase 1 study of veliparib administered in combination with standard doses of cisplatin and etoposide was conducted in treatment naïve- patients with extensive stage SCLC (n = 9). [37] The recommended Phase 2 dose of veliparib was 100 mg. The preliminary efficacy in 7 evaluable patients were: 1 CR (14.3%), 4 PR (57.1%), and 2 SD (28.6%). Grade 3-5 hematologic AEs included neutropenia, leukopenia, lymphopenia, and thrombocytopenia.

PARP inhibitor Monotherapy Treatment in Indications with Homologous Recombination Deficiency

High frequency of HRD has been identified in subsets of ovarian cancer, and in uterine, lung squamous, esophageal, sarcoma, bladder, lung adenocarcinoma, head and neck and gastric cancer samples. [38, 39]

A limited number of studies have evaluated the efficacy of niraparib, rucaparib, talazoparib and olaparib in different indications with HRD, as assessed by a variety of methods and demonstrated antitumor activity in HRD+ patients even in the absence of *BRCA 1/2* mutations.

Niraparib treatment of advance stage ovarian cancer patients (QUADRA study) elicited an ORR of 17.5% (N=126) in HRD+/ *BRCA* wild type patients as determined by the Myriad myChoice® assay, irrespective of platinum sensitivity. [40]

Second and 3rd line, platinum sensitive ovarian cancer patients determined to have loss of heterozygosity (LOH) high/*BRCA* wild type disease by the Foundation Medicine NGS test and treated with rucaparib (ARIEL 2 trial) also showed an ORR= 29.3% (n=82). [41] Rucaparib treatment of HER2 negative metastatic breast cancer patients with LOH high or somatic *BRCA* mutant tumors as assessed by Foundation medicine NGS resulted in an ORR of 10.8% (N=37). [42]

Olaparib treatment of metastatic pancreatic cancer patients without genomic *BRCA 1/2* mutations, but with mutations in DNA damage response genes (based on historical data) elicited an ORR of 21.8% (N=31). [61] Patients with biliary tract, bladder, colorectum, lung, esophageal and uterine cancer with genomic *BRCA1/2* mutations treated with olaparib showed an ORR of 8.3% (N=12). [62]

Finally, talazoparib treatment of patients with solid tumors harboring mutations in a selected panel of genes (*PALB2, CHEK2, ATM, NBN, BARD1, BRIP1, RAD50, RAD51C, RAD51D, MRE11, ATR, PTEN, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCL*) resulted in an ORR of 15% (N=20). [43]

1.3. PARP Inhibitors and Temozolomide (TMZ)

Temozolomide (TMZ) induces apoptosis and cell death by methylating guanine at the O^6 position, initiating a double-strand break in the DNA and cell cycle arrest. PARP1 and PARP2 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 do not contribute to TMZ cytotoxicity. The first step of the BER process is the excision of the modified base by N-methylpurine glycosylase (MPG). The subsequent removal of the basic residues by apurinic/apyrimidinic endonuclease results in the generation of DNA damage that is finally repaired by the coordinate intervention of PARP1, DNA polymerase, XRCC1, and ligase III. Inhibition of PARP activity hampers PARylation of PARP1 and PARP2, interrupting the completion of the repair process mediated by BER. [44]

Therefore, increased anti-tumor activity due to the combination of PARP inhibition and TMZ is the consequence of increased DNA damage that eventually 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. [45, 46] This might further contribute to sensitizing cancer cells to the TMZ and PARP inhibitor combination.

Several clinical studies have been conducted with PARP inhibitors (olaparib, rucaparib, veliparib, and talazoparib) in combination with TMZ. [47, 48, 49, 50, 51, 52, 53, 54] 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 (DLT) and observed anti-tumor activity was only modest.

In a single-arm Phase 2 study, veliparib was tested in combination with TMZ in 41 women with advanced TNBC (8 with *BRCA* germline mutation) and the overall response rate was 7% across the entire study population. However, patients with *BRCA* mutations had a 37.5% overall response rate. [47]

Veliparib (40 mg BID) in combination with TMZ was also studied in patients with mCRPC. The primary endpoint was a ≥ 30% decrease in PSA level. [48] Modest activity was seen in the 25 evaluable patients; 2 (8%) had a confirmed PSA response, 13 (52%) had stable PSA levels, the median PFS was 9 weeks (95% CI: 7.9-17) and the median overall survival was 39.6 weeks (95% CI: 26.6-not estimable). The most common Grade 3/4 adverse events occurring in >10% of patients were thrombocytopenia and anemia.

In a recent study talazoparib, a PARP inhibitor with very good DNA-trapping activity, was used in combination with TMZ in patients with advanced malignancies. In contrast to previous studies, mentioned above, standard doses of talazoparib (0.5 to 1 mg) were administered with low doses of TMZ in patients with non-*BRCA1/2*-mutated cancers. [54] The starting dose of TMZ was 25 mg/m^2, approximately 12.5% of the therapeutic dose, and the MTD was identified 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 PR or SD. 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.

Continuous dosing of TMZ is thought to enhance the antitumor activity through sustained depletion of the DNA repair protein O6-alyklyguanine DNA alkyltransferase. [55] Several studies have used continuous dosing of TMZ in patients with solid tumors, lymphoma, melanoma, and glioblastoma. [55, 56, 57, 58] In these studies, the dose of TMZ ranged from a daily dose of 150 mg/m^2 for 5 days during each 28-day cycle to 75 mg/m^2 daily for 6 to 7 weeks and 50 mg/m^2 daily up to 1 year. In a study of continuous TMZ (75 mg/m^2 daily for 6 weeks), the most common AEs were lymphopenia (60%). Of note, 2 (2%) patients had opportunistic disease (pneumocystis pneumonia and aspergillus pneumonia). [57] In a study of continuous TMZ (50 mg/m^2 daily for up to 1 year), the most common Grade 3/4 AEs were nausea and vomiting; the most common hematological adverse event was Grade 3 lymphocytopenia, and Grade 1/2 opportunistic infections (thrush) but no pneumocystis pneumonia. [58]

1.4. Nonclinical Data

1.4.1. Nonclinical Data on Pamiparib

Pamiparib is a highly potent and selective inhibitor of PARP1 and PARP2 that sets itself apart from other PARP inhibitors by combining potent DNA-trapping activity with good brain penetrance. In addition, pamiparib has shown anti-tumor activity against a number of cell lines harboring *BRCA* gene mutations or homologous recombination defects as well as *in vivo* models.

1.4.1.1. Nonclinical Safety Data for Pamiparib

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* human ether-a-go-go related gene (hERG) channel activity assays and *in vivo* studies of cardiovascular function in dogs, as well as central nervous system (CNS) 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 (CHO) 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 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 are planned as they were not considered essential because of its genotoxicity and bone marrow inhibition.

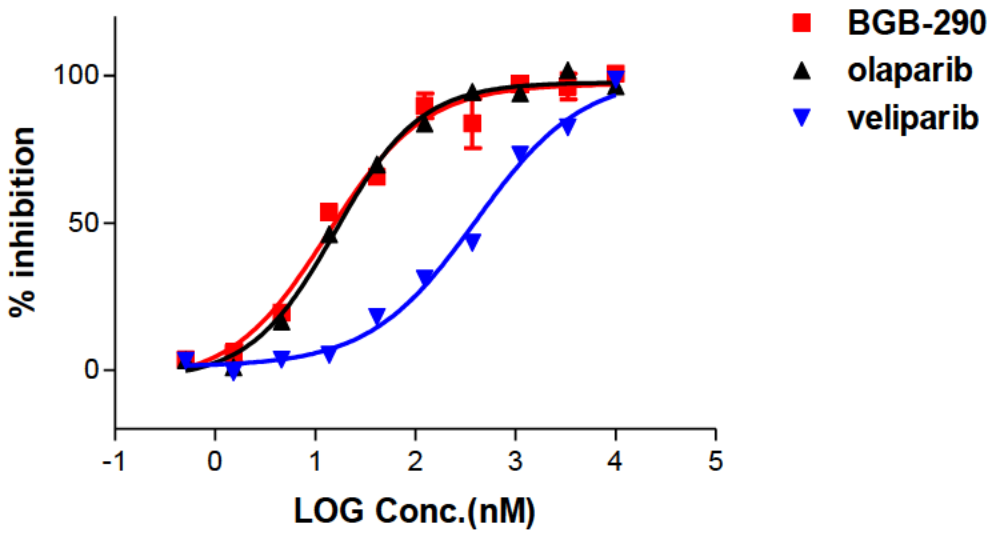
There was no apparent inhibition of pamiparib on hERG channel as the half inhibitory concentration (IC_{50}) was 12.4 μM; for comparison, the IC_{50} of the positive control amitriptyline was 1.9 μM. No effects on blood pressure, heart rate, or electrocardiograms (ECGs) were noted in telemetry-instrumented conscious dogs. No effects on CNS or respiratory functions were noted in Sprague-Dawley rats. No abnormal changes in the cardiovascular, CNS, and respiratory systems 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. Please refer to the Investigator's Brochure (IB) for additional information. [59]

1.4.1.2. PARP Trapping Data for Pamiparib

A subset of PARP inhibitors are 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. [60] The DNA-trapping activity of pamiparib was measured by a fluorescence polarization (FP) binding assay similar to the method described in the literature. [60] Fluorescence-labeled nicked DNA was pre-incubated with PARP1and PARP inhibitors (pamiparib, olaparib, and veliparib). Nicotinamide adenine dinucleotide (NAD) was added to initiate 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

EC_{50} = half maximal effective concentration; nM = nanomole

1.4.1.3. 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%.

1.4.1.4. Nonclinical Anti-Tumor Activity Data for Pamiparib

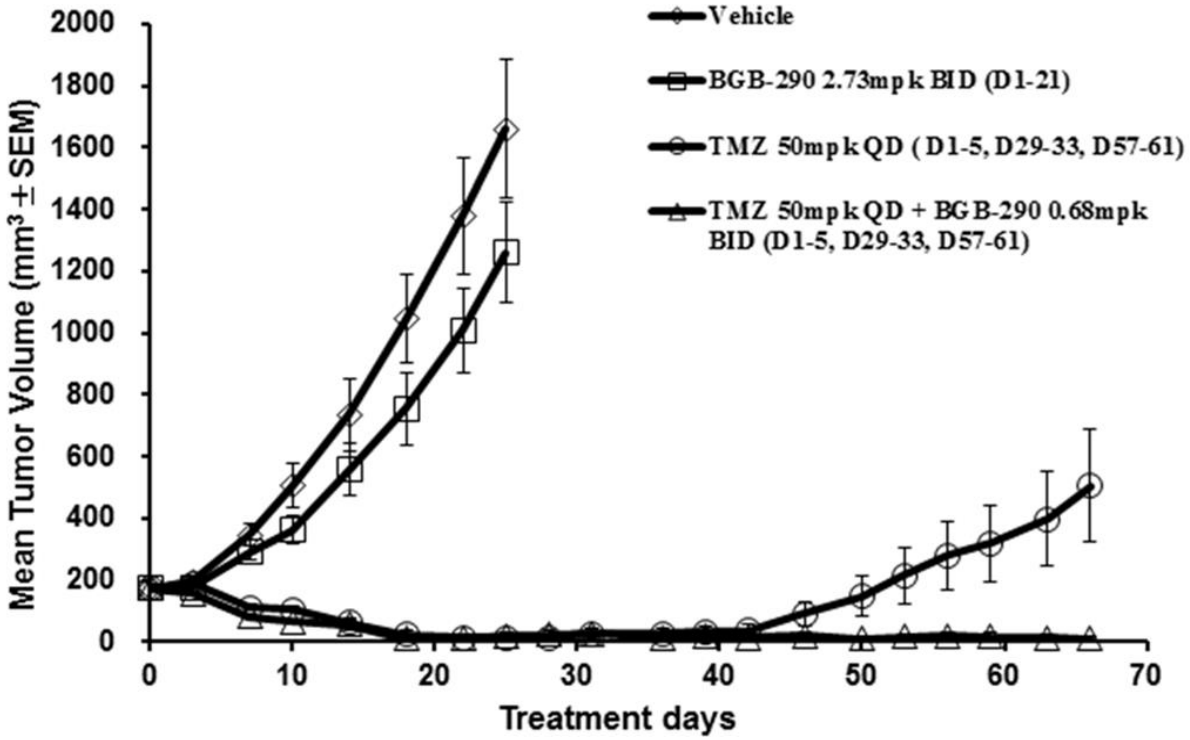
Pamiparib as a single agent has demonstrated excellent *in vitro* activity against tumor cell lines with defects of the homologous repair pathway. *In vivo*, pamiparib showed strong anti-tumor activity against a *BRCA1*-mutant mouse xenograft model (MDA-MB-436 breast cancer) and was 16-fold more potent than olaparib. In a pharmacokinetic (PK)/pharmacodynamic (PD) study, oral 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.

Please refer to the IB for additional information. [59]

1.4.2. Nonclinical Data on Pamiparib in Combination with TMZ

The anti-proliferative effect of pamiparib in combination with TMZ was evaluated in 8 human GB 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 half maximal effective concentration (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 2). 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 three 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 anti-tumor activity and delayed resistance.

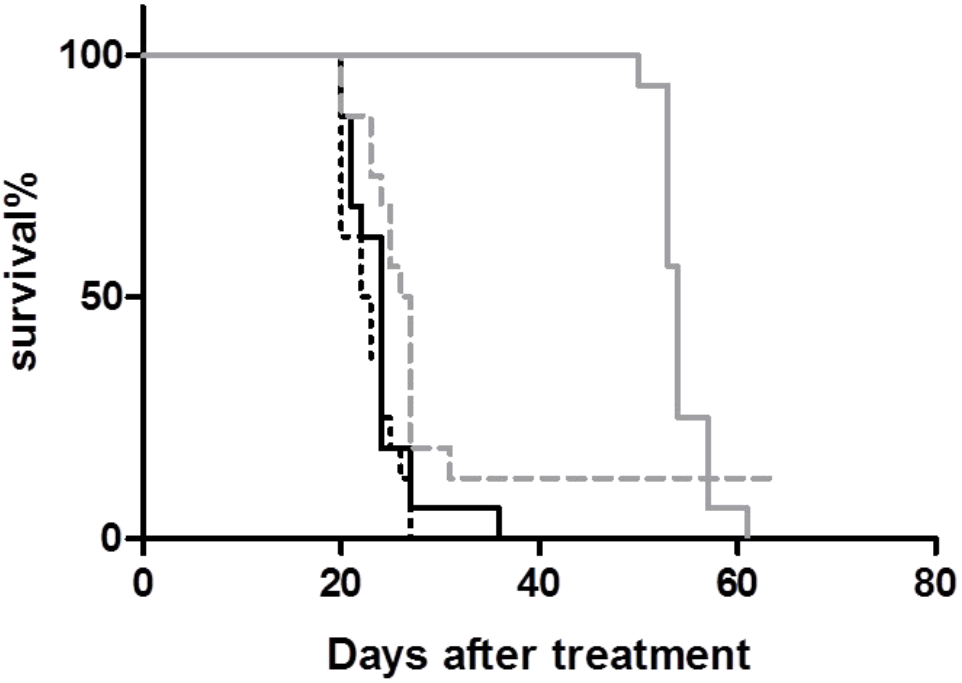
Figure 2: Combination Activity of Pamiparib and Temozolomide in H209 Small Cell Lung Cancer Xenograft Model



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; SEM = standard error of the mean.

Given the significant brain penetrance of pamiparib, its activity was further explored in an intracranial tumor model in nude mice for H209-T DCLC xenografts (Figure 3). 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 alone ($p < 0.01$), with a median survival of 54 days. The result suggests pamiparib in combination with TMZ can overcome TMZ resistance in this intracranial model.

Figure 3: 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

1.5. Clinical Data for Pamiparib

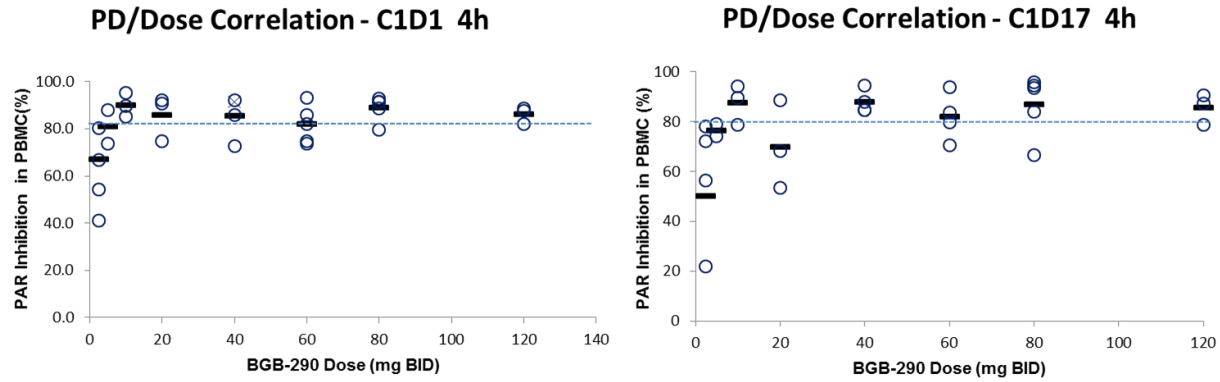
1.5.1. Pharmacokinetics of BGB-290-AU-002

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 (the area under the concentration-time curve [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 hours, 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 an approximately 2-fold accumulation.

1.5.2. Exploratory Biomarker Data

The PAR formation from peripheral-blood mononuclear cells (PBMCs) was detected by ELISA to explore the dose-responsive PD activity in the Pamiparib Phase 1 monotherapy study. Blood samples for PK and isolation of PBMCs were obtained at baseline, on day 1 (pre-dose), and days 1 and 17 (4 hours post-dose) of Cycle 1 (Figure 4).

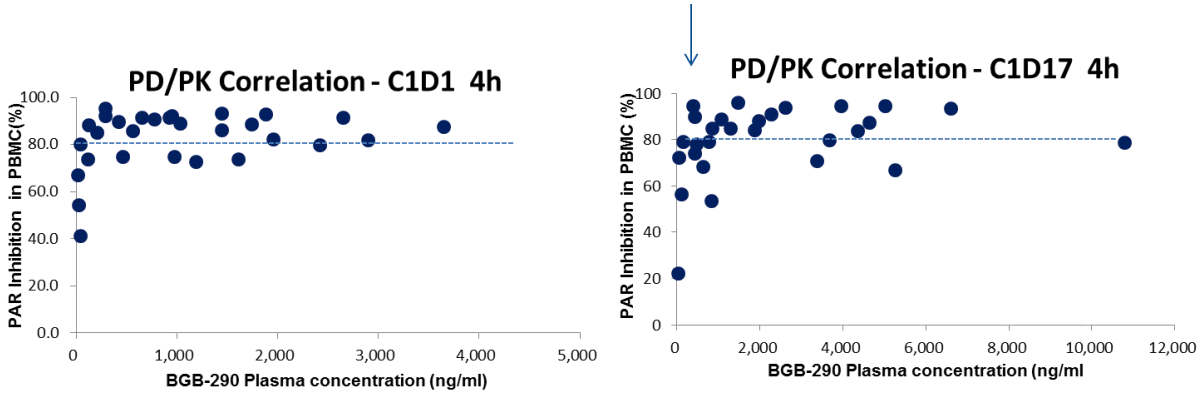
Figure 4: PAR inhibition was plotted against BGB-290 dose at the time of PBMC collection



PBMC = peripheral blood mononuclear cell

The PD activity at 4h post-dose on D1 and D17 were reported as percentage PAR inhibition from pre-dose. PD/PK correlation analyses were conducted from 30 patients who received doses of 2.5, 5, 10, 20, 40, 60, 80, and 120 mg BID. Robust PAR inhibition in PBMCs was observed even at the first dose level of 2.5mg BID, consistent with the clinical activity observed, and appeared to be maximal at doses ≥ 10mg BID. The PD activity also increased in an exposure-dependent manner with sustained PAR inhibition in PBMCs being observed at steady state exposures expected in patients treated with 10 mg BID, or higher, doses (Figure 5, arrow).

Figure 5: PAR inhibition was plotted against BGB-290 drug level in the plasma at the time of PBMC collection



PBMC = peripheral blood mononuclear cell

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

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

The study was conducted in 5 Australian study centers and preliminary data for 45 patients are available (cut-off date of 30 September 2016).

The preliminary safety data indicate the most frequent related AEs (≥ 10% of patients) assessed as related 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, 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 percent of the patients experienced a 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 BGB-290: anemia (n=5), neutropenia (n=3), hypophosphatemia (n=1), nausea (n=1), and fatigue (n=1). Serious AEs reported as related to BGB-290 included anemia (n=2) and nausea (n=1).

The DLT of BGB-290 was persistent Grade 2 nausea despite optimal standard medical therapy observed in the 120 mg BID cohort (n=2) and in one patient each in the 40 mg and 80 mg BID cohorts. The MTD of BGB-290 was 80 mg PO BID.

Ten patients achieved either complete (n=2) or partial (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).

Based upon the overall safety, efficacy, and PK profile of pamiparib, the dose for further investigation was determined to be 60 mg PO BID.

1.6. Study Rationale

Alkylating agents such as TMZ cause SSBs in DNA, which leads to the recruitment of PARP1 and 2 to bind to the site of damage to repair the SSBs. PARP inhibitors are a class of drugs designed to compete at the PARP enzyme binding site and act as catalytic inhibitors, leading to accumulation of unrepaired SSBs. [60] Thus PARP inhibition enhances the cytotoxicity of the BER pathway, and therefore, enhances TMZ cytotoxicity. 6261, 62]

The study populations proposed for the expansion phase of this study are patients with tumors likely to harbor DNA damage repair deficiencies susceptible to treatment with PARP inhibitors. It is hypothesized that increased DNA damage by TMZ and PARP inhibition will provide synergism resulting in an increased anti-tumor activity in advanced solid tumors. Furthermore, the clinical data for the use of PARP inhibitors in patients with TNBC, ovarian cancer, mCRPC, gastric cancer, and SCLC discussed in Section 1.2, along with the data describing the use of PARP inhibitors plus TMZ in Section 1.3, supports evaluating pamiparib in combination with TMZ in this patient population.

1.6.1. Rationale for Dose Selection of Pamiparib

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 below the regimen for this study (10 mg versus 60 mg BID). The dose of pamiparib chosen for this study is based on the recommended Phase 2 dose (RP2D) determined in the Phase 1 monotherapy study, BGB-290-AU-002, discussed in Section 1.5.

1.6.2. Rationale for Dose Selection of Temozolomide (TMZ)

As discussed in Section 1.3, previous combination studies using standard doses of TMZ and increasing low doses of PARP inhibitors had only modest anti-tumor effects and increased cytopenia. A recent study that used sub-therapeutic doses of TMZ with standard doses of talazoparib showed more promising anti-tumor effects and a better safety profile [36]. Similarly, this study is designed to use the RP2D of pamiparib (60 mg BID) with low doses of TMZ, starting from 40 mg/day up to 120 mg/day (23 mg/m^2/day to 69 mg/m^2/day) or higher which corresponds to 15%-46% of its recommended dose (150mg/m^2/day) when administered daily for 5 days every 28 days (see Section 6.1 , Table 2). In addition, continuous dosing of TMZ will start at 40 mg/day and would potentially increase up to 120 mg/day of TMZ, which translates to 30% and 92%, respectively, of a daily dose of 75 mg/m^2. [56, 59]

In summary, pamiparib is a promising selective inhibitor of PARP1 and PARP2 that exhibits excellent DNA-trapping activity making it an excellent candidate to determine the effects of combining PARP inhibition with TMZ in these patient populations.

1.7. 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 a partial overlap with the safety profile of TMZ. Therefore, patients of this study may experience AEs typical for these study drugs at a higher frequency and/or severity. In addition, patients may encounter AEs that are uniquely caused by the novel combination(s). However, with the lower doses of TMZ being used in this study, it is possible there could be fewer myelosuppressive-related AEs than previously seen in other studies using TMZ in combination with PARP inhibitors.

Myelodysplastic syndrome and acute myeloid leukemia (AML) have been reported in a small number (< 1%) of patients treated with PARP inhibitors, especially in patients harboring a germline *BRCA* mutation. [63] Typically, patients who develop MDS and AML while on PARPi therapy had a history of extensive previous chemotherapy and some had a history of previous cancer or bone marrow abnormalities. To date, there have been no reports of MDS or AML in patients treated with pamiparib and no fatal drug reactions. Patients in this study will be monitored monthly for hematological toxicities and events of MDS and AML will be reported as serious AEs (SAEs).

Preliminary data show that pamiparib appears to be generally well tolerated in patients with advanced solid tumors. The safety profile for single-agent pamiparib is similar to that of other PARP inhibitors. Given the dire prognosis of the patients that will be enrolled in this study and

the limited treatment options, the risk of combining pamiparib with 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 Section 1.1 and Section 1.6, scientific rationale and supportive data are strong for combining PARP inhibitors with TMZ in TNBC, ovarian cancer, mCRPC, and other solid tumors with homologous recombination deficiency as well as in SCLC and gastric cancer.

1.8. 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 in accordance with Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES

2.1. Primary Objectives

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

2.2. Secondary Objectives

- To characterize the pharmacokinetics (PK) of pamiparib and TMZ

2.3. Exploratory Objectives

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

3. STUDY ENDPOINTS

3.1. Primary Endpoints

- Dose Escalation Phase: Incidence and nature of DLTs
- Incidence, nature, and severity of AEs, graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), v4.03
- Objective response rate (ORR), as assessed using RECIST v1.1

3.2. Secondary Endpoints

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

3.3. Exploratory Endpoints

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

4. STUDY DESIGN

4.1. Summary of Study Design

This is an open-label, multi-center Phase 1b study to evaluate the combined use of pamiparib, a PARP inhibitor, with a DNA-alkylating agent, TMZ, in patients with locally advanced and metastatic solid tumors. The study consists of a dose escalation phase and a dose expansion phase. The dose escalation phase of the study will evaluate the safety, tolerability, preliminary efficacy, and PK, in addition to determining the MTD and/or MAD for the combination. In the dose expansion phase of this study, the safety, preliminary efficacy, and PK profile of the combination will be further evaluated in specific patient populations. Preliminary biomarkers for efficacy will also be explored during both phases of the study.

Dose Escalation:

The dose escalation phase of the study consists of a modified 3+3 dose escalation scheme utilizing a fixed dose of pamiparib in combination with escalating doses of TMZ. There will be two arms that will undergo dose escalation independently. In Arm A, TMZ will be administered once a day during Days 1 to 7 of each 28-day cycle (pulsed). In Arm B, TMZ will be administered once a day continuously during each 28-day cycle.

Dose Expansion:

The dose expansion phase of the study will further evaluate the safety and anti-tumor activity of pamiparib in combination with TMZ at the dose and schedule that will be chosen based on all data available from the dose escalation phase.

It is expected that approximately 250 patients will be enrolled in the entire study. Patients will be enrolled in 6 different cohorts based on their disease characteristics and/ or HRD status as described in Section 4.3; Enrollment into these cohorts will occur simultaneously and independently of each other. Each expansion cohort will enroll up to 20-25 patients each and may enroll additional patients based on emerging data, but the total patients enrolled in the study will not exceed 250 patients.

Adverse events (AEs) that occur during and after the treatment period with study drug(s) will be followed and documented as outlined in Section 7.4 and Section 10. AEs will be graded according to NCI CTCAE v4.03.

Pharmacokinetic analysis will be performed for both pamiparib and TMZ during Cycle 1. Biomarker analysis will include but is not limited to germline *BRCA1/2* mutations, DNA HRD status, and somatic mutation analysis.

Anti-tumor activity will be evaluated by the treating investigator using standard RECIST v1.1 criteria (Appendix 5). Tumor response will also be evaluated according to the Gynecologic Cancer Intergroup (GCIG) criteria for patients with ovarian cancer. In addition, the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria will be used for patients with prostate cancer.

Patients who, at the time of progression, have an ongoing AE that leads to treatment discontinuation, will be followed until the event resolves, the investigator assesses the event as stable, the patient is lost to follow-up, or the patient starts a different anti-tumor therapy. If a patient discontinues study drug due to reasons other than disease progression or death, then tumor assessments should continue to be performed following the scheduled assessment plan until the start of new anticancer therapy, disease progression, death, lost to follow-up, or withdrawal of consent to efficacy follow-up.

In the absence of unacceptable toxicities or disease progression, patients will be offered continued study treatment of BGB-290 plus TMZ. Regardless of discontinuation of one or more study drugs, patients should continue on study with regular follow-up (Section 8.5). Patients who have discontinued all study drugs should return to the clinic for an end-of-treatment (EOT) visit within 7 days after the last study treatment (Section 8.4). After the EOT visit, patients should have regular follow-up for safety, efficacy, and survival as outlined in Section 8.5.

Study procedures and assessments are further detailed in Section 7 and Section 8, and a Schedule of Assessments can be found in Appendix 1 Table 1.

4.2. Details of Dose Escalation

4.2.1. Starting Dose and Dose Escalation Approach

The dose escalation phase consists of two arms as follows:

> **Arm A** (pulse TMZ dosing): continuous pamiparib (60 mg BID) in combination with increasing doses of TMZ (flat doses of 40, 80, 120 mg QD and higher, if tolerated) administered on Days 1 to 7 of each 28-day cycle
>
> **Arm B** (continuous TMZ dosing): pamiparib (60 mg BID) in combination with increasing doses of TMZ (flat doses of 20, 40, 80, 120 mg QD and higher, if tolerated) administered continuously.

A minimum of three patients will be enrolled in Arm A, Dose Level 1, before patients are enrolled into Arm B, Dose Level 1. Subsequently, enrollment and dose escalation decisions for the two arms will occur independently of each other.

The dose for pamiparib will be the RP2D of 60 mg PO BID ('full-dose' pamiparib) based on the rationale outlined in Section 1.6. 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 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 nor will it exceed the approved daily dose at the corresponding schedule.

Once the MTD has been determined in Arm A (pulse dosing) and taking into consideration all data available for Arm B at that time, further dose escalation may be pursued for Arm A by extending the time window of TMZ administration by no more than one additional week per dose escalation step. For example, TMZ administration at the MTD dose level may be extended to Days 1 to 14 and then to Days 1 to 21 following dose escalation rules outlined in Section 4.2.2.

If the MTD is exceeded with the starting dose of TMZ, then a dose level of 20 mg QD TMZ (Dose Level -1) may be explored. (Table 1).

Table 1: Dose Escalation Scheme for Pamiparib plus TMZ

	Arm A (Pulse Dosing of TMZ)		Arm B (Continuous Dosing of TMZ)	
Dose Level	Pamiparib Continuous	TMZ Days 1 to 7, every 28 days	Pamiparib Continuous	TMZ Continuous
-1	60 mg BID	20 mg QD	**60 mg BID**	**20 mg QD***
1	**60 mg BID**	**40 mg QD***	60 mg BID	40 mg QD
2	60 mg BID	80 mg QD	60 mg BID	80 mg QD
3	60 mg BID	120 mg QD	60 mg BID	120 mg QD
≥4	60 mg BID	Increase by ≤ 50% each time until MTD reached	60 mg BID	Increase by ≤50% each time until MTD reached

*Starting dose; BID = twice daily; MTD = maximum tolerated dose; QD = once daily; TMZ = temozolomide

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 after discussions with all investigators. For example, alternative regimens for pamiparib dosing may be explored such as lower doses of pamiparib continuously or full-dose pamiparib for Days 1 to 21 of each 28-day cycle.

Depending on emerging safety data from this and other pamiparib Phase 1 studies, the pamiparib regimen may be switched to QD (≤ 120 mg QD) for one or both of the arms at any time during or after dose escalation. The first QD regimen of pamiparib will be at a dose level already cleared for the BID regimen.

4.2.2. Rules for Dose Escalation

Dose escalation will occur in accordance with the following modified 3 + 3 dose escalation rules:

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

- If none of the first three evaluable patients enrolled in a given cohort experience a DLT, dose escalation may proceed.
- If one of the first three evaluable patients enrolled in a given cohort experiences a DLT, additional patients (for a minimum of six evaluable patients) will be enrolled in that cohort.

  - If less than one third- of evaluable patients in a given cohort experiences a DLT (e.g., DLTs in fewer than two of six patients), escalation will proceed to the next higher dose level.

If a DLT is observed in at least one-third or more of patients (e.g., two or more of up to six patients), the MTD will have been exceeded, and dose escalation will be stopped.

- Additional patients (for a minimum of six evaluable patients) will be assessed for DLTs at the preceding dose level (if a minimum of six evaluable patients had not already been assessed at that dose level).
- 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 (e.g., DLTs in fewer than two of six patients) will be declared the MTD.

If less than one third- of evaluable patients (e.g., DLTs in fewer than two of six 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 TMZ, including AEs, laboratory assessments, and PK analyses, will be reviewed by the Medical Monitor, investigators, PK scientist, and clinical trial manager. 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 drug administration for each arm and all dose levels.

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 receive ≥70% of scheduled pamiparib and TMZ 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 dose escalation.

4.2.4. Definition of Dose-Limiting Toxicity

A DLT is defined as one of the following toxicities occurring during the DLT assessment window 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 > 7 days
- Grade 4 anemia
- Grade ≥ 3 total bilirubin or hepatic transaminases (alanine aminotransferase [ALT or SGPT] or aspartate aminotransferase [AST or SGOT]) with the following exceptions:
  - For patients with Grade 1 hepatic transaminase levels at baseline, a hepatic transaminase level of > 7.5 x upper limit of normal (ULN) will be considered a DLT.
  - For patients with Grade 2 hepatic transaminase levels at baseline, a hepatic transaminase level > 10 x ULN will be considered a DLT.

4.3. Expansion Cohorts

The dose expansion phase of the study will begin once the safety and tolerability have been reviewed for the dose escalation cohorts and the preferred dose and schedule of pamiparib plus TMZ has been determined. Approximately 200 patients will be enrolled in the dose expansion phase with approximately 20-25 patients enrolled into each cohort. Enrollment into each cohort will occur in parallel.

Expansion Cohort 1: Patients with platinum-sensitive high-grade epithelial, non-mucinous, ovarian cancer, fallopian cancer, or primary peritoneal cancer with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation or with DNA HRD.

Expansion Cohort 2: Patients with TNBC with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation or with DNA HRD who have received 0-1 prior platinum-containing treatment in any treatment setting and treated with ≤ 3 prior regimens.

Expansion Cohort 3: Patients with mCRPC with either known deleterious or suspected deleterious germline or somatic *BRCA1/2* mutation or with documented HRD.

Expansion Cohort 4: Patients with extensive-stage SCLC who have been treated with ≤ 2 prior regimens.

Expansion Cohort 5: Patients with gastric or gastroesophageal junction cancer who have been treated with ≤ 2 prior regimens.

Expansion Cohort 6: Patients with non-squamous and squamous NSCLC, esophageal cancer, squamous head and neck cancer, or soft tissue sarcomas (specific subtypes: undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, dedifferentiated liposarcoma, myxofibrosarcoma) whose tumors are HRD+ as determined centrally by the Myriad myChoice® HRD Plus assay. Patients with NSCLC, esophageal and head and neck cancer may have received at least 1 but no more than 3 prior lines of therapy. Patients with soft tissue sarcoma may have received at least 1 but no more than 3 prior lines of

therapy OR no therapy if, in the opinion of the investigator, standard of care first line therapy is not appropriate.

The safety and PK assessments, as well as the rules for continued dosing in the cohort-expansion phase, will be identical to those in the dose escalation phase.

Each cohort will be evaluated independently for study endpoints and can be closed due to lack of enrollment, anti-tumor activity or other reasons. Cohorts may be also further expanded based on clinical emerging data.

If the frequency of Grade ≥ 3 toxicities or other unacceptable chronic toxicities in the cohort-expansion phase suggests 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 20 patients) into an expansion cohort at a lower dose level.

5. STUDY POPULATION

5.1. Inclusion Criteria

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

All Cohorts

1. Patient has voluntarily agreed to participate by signing an informed consent
2. Male or female and ≥ 18 years of age at the time of informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
4. Ability to swallow whole capsules
5. Patients who have histologic or cytologic-confirmed malignancy that has progressed to the advanced or metastatic stage
6. Agree to provide archival tumor tissue
   a. ***Dose Escalation Phase****:* If available, agreement to provide archival tumor tissue for exploratory biomarker analyses
   Note: If archival tumor tissue is not available, an optional fresh biopsy is highly recommended.
   b. ***Dose Expansion Phase***: patients enrolled in the HRD+ cohorts must provide archival tissue or fresh biopsy (if archival tissue is not available) for prospective central assessment of HRD status. Other cohorts may provide tissue, if available, for retrospective analysis.
7. Patients must have adequate organ function as indicated by the following screening laboratory values (obtained ≤ 2 weeks prior to Day 1):
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   b. Platelets ≥ 100 x 10^9/L (Note: Criterion must be met without a transfusion within the 2 weeks prior to obtaining the sample)
   c. Hemoglobin ≥ 10 g/dL or ≥ 6.1 mmol/L (Note: Criterion must be met without a transfusion within the 2 weeks prior to obtaining the sample)
   d. Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated creatinine clearance ≥ 50 mL/min (calculated using the institutional standard method)
   e. Total serum bilirubin ≤ 1.5 x ULN (total bilirubin must be < 4 x ULN for patients with Gilbert's syndrome or if indirect bilirubin concentrations are suggestive of extrahepatic source of elevation)
   f. Aspartate and alanine aminotransferase (AST and ALT, respectively) ≤ 3 x ULN OR ≤ 5 x ULN for patients with liver metastases
8. Female patients of childbearing potential and female partners of male study patients must agree to practice highly effective methods of birth control (Appendix 2) for the duration of the study and for ≥ 6 months after the last dose of study drug. In addition, non-sterile male patients must agree to practice highly effective methods of birth control (Appendix 2) and avoid sperm donation for the duration of the study and for ≥ 6 months after the last dose of study drug.

9. Willingness and ability to comply with all protocol-specified requirements

Dose Escalation Phase only

10. Patient must have disease that is either measurable or evaluable per RECIST v1.1 criteria.

Dose Expansion Phase only

11. Patient must have measurable disease per RECIST v1.1 criteria (except where noted below).

    Note: tumor lesions used for freshly acquired biopsies should not be included as target lesions unless there are no other suitable target lesions available

12. Ovarian Cancer (Expansion Cohort 1)
    a. Patients must have received at least one line of platinum-containing therapy in the advanced or metastatic setting.
    b. Patients must not have progressed or have recurrent disease within 6 months of the completion of the last platinum-containing regimen.
        - Note: Patients can receive additional therapy after the last platinum-containing regimen as long as the criteria for platinum-sensitivity is met.
    c. Patients with known or suspected deleterious mutations in BRCA1 or BRCA2 HRD+, regardless of the molecular signature result.
        - If HRD or BRCA1/2 mutation status is unknown or has not been previously evaluated, the patient must undergo tissue screening using the Myriad myChoice® HRD diagnostic test to determine eligibility.
13. Triple-Negative Breast Cancer (Expansion Cohort 2)
    a. Patients with known or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD+, regardless of the molecular signature result.
        - If HRD or BRCA 1/2 mutation status is unknown or has not been previously evaluated, the patient must undergo tissue screening using the Myriad myChoice® HRD diagnostic test to determine eligibility.
    b. 0-1 prior platinum-containing treatment in any treatment setting
        - Note: Patients could have received additional therapy after the last platinum-containing regimen as long as the other eligibility criteria are met.
    c. Received ≤ 3 prior lines of therapy in the advanced or metastatic setting
14. Metastatic Castration-Resistant Prostate Cancer (Expansion Cohort 3)
    a. Patients with known or suspected deleterious mutations in *BRCA1* or *BRCA2* are classified as HRD+, regardless of the molecular signature result.
        - If HRD or *BRCA1/2* mutation status is unknown or has not been previously evaluated, the patient must undergo tissue screening using the Myriad myChoice® diagnostic test to determine eligibility.

b. The patient may be either chemotherapy-naïve or have previously had no more than two taxane-based chemotherapy regimens including docetaxel and carbazitaxel. If docetaxel is used more than once, this will be considered as one regimen.
c. The patient may be pre- or post-treatment with a novel androgen receptor targeted agent (e.g., abiraterone and/or enzalutamide).
d. At least 2 weeks since the completion of prior flutamide, bicalutamide, and nilutamide, or enzalutamide and abiraterone treatment
e. At least 2 weeks from any radiotherapy, with the exception of a single fraction of radiotherapy for the purposes of palliation (confined to one field)
f. Documented prostate cancer progression as assessed by the investigator with one of the following:

- Prostate-specific antigen (PSA) progression defined by a minimum of 3 rising PSA levels with an interval of ≥ 1 week between each determination. The PSA value at the screening visit should be ≥ 2 µg/L (2 ng/ml).
- Radiographic progression of soft tissue disease by modified RECIST v1.1 criteria
- Surgically or medically castrated. The testosterone levels do not need to be checked as long as the patient has been on chemical castration or undergone surgical castration for > 4 months. In all cases, the luteinizing hormone-releasing hormone (LHRH) antagonist/agonist is to be continued in these patients.
- Patients with only non-measurable bone lesions must have either progression with 2 or more new lesions or have PSA progression within the 6-week period before study drug administration.

15. Extensive Stage Small Cell Lung Cancer (Expansion Cohort 4)
    a. Received ≤ 2 prior lines of therapy
16. Gastric/Gastroesophageal Junction Cancer (Expansion Cohort 5)
    a. Received ≤ 2 prior lines of therapy
17. HRD+ Solid Tumors, Multiple Indications (Expansion Cohort 6)
    a. Patient has histologic or cytologic-confirmed advanced (metastatic and/or unresectable)
        - non-squamous non-small cell lung cancer (NSCLC)
        - squamous NSCLC
        - esophageal cancer
        - squamous head and neck cancer
        - soft-tissue sarcomas (undifferentiated pleomorphic sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor, dedifferentiated liposarcoma, myxofibrosarcoma)

b. Patients must have tumors with homologous recombination deficiency (HRD+) as centrally determined by the Myriad myChoice® HRD Plus assay irrespective of their known molecular signature
c. Patients with nonsquamous NSCLC, squamous NSCLC, esophageal cancer, squamous head and neck cancer must have received at least 1 but not more than 3 prior lines of therapy.
d. Patients with soft tissue sarcoma must have received at least 1 but no more than 3 prior lines of therapy. Treatment naïve patients may be allowed if, in the opinion of the investigator, available standard of care first line therapy is not appropriate

5.2. Exclusion Criteria

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

1. Known hypersensitivity to any temozolomide (TMZ) component or to dacarbazine (DTIC)
2. Prior treatment with a PARP inhibitor
3. Received chemotherapy, biologic therapy, immunotherapy, or investigational agent within 3 weeks prior to Day 1 (or ≤ 5 half-lives, whichever is shorter) (unless otherwise noted in the Inclusion Criteria)
4. Patients who are considered to be refractory to platinum-based therapy (e.g., progressive disease at the first tumor assessment while receiving platinum treatment) (for patients in dose expansion phase only)
5. Have any unresolved acute effects of any prior therapy of Grade 2 or higher, except for AEs not constituting a safety risk by investigator judgment
6. Had a major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks 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
7. Have 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.
8. Patient who has received local radiotherapy of non-target lesions for local symptom control within the last 4 weeks must have recovered from any adverse effects of radiotherapy before recording baseline symptoms.
9. Have untreated leptomeningeal or brain metastasis. Patients with previously treated brain metastases are eligible if the metastases have shown no progression on brain computed tomography (CT) or magnetic resonance imaging (MRI) over at least 4 weeks, the

patients have no symptoms due to the brain metastases, and the patients have been off corticosteroids for ≥ 2 weeks.

10. Have active infection requiring systemic treatment
11. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection as follows:
    - Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL should be excluded. Note: Inactive HBsAg carriers and patients with treated and stable hepatitis B (HBV DNA < 500 IU/mL) can be enrolled. Patients receiving antivirals at screening should have been treated for > 2 weeks before the first dose of study drug(s).
12. Have 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 (Appendix 3) ≤ 6 months prior to Day 1
    - Grade ≥ 2 ventricular arrhythmia ≤ 6 months prior to Day 1
    - Cerebral vascular accident (CVA) ≤ 6 months prior to Day 1
13. Have an active inflammatory gastrointestinal disease, chronic diarrhea, or had previous complete gastric resection or lapband surgery

    Note: Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed (assuming no drug interaction potential).
14. Use or have anticipated need for food or drugs known to be strong or moderate cytochrome P450 (CYP)3A inhibitors or strong CYP3A inducers ≤ 10 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1(Appendix 4)
15. Are pregnant or nursing (females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1)
16. Have hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption

6. STUDY TREATMENT

6.1. Study Drugs

6.1.1. Pamiparib (BGB-290)

Patients will receive pamiparib as 10 mg, 20 mg, 40 mg, or 60 mg capsules, depending on dose level and capsule availability.

6.1.1.1. Packaging and Labelling

Pamiparib capsules are provided in a container with a child-resistant closure and labelled in accordance with all applicable local regulatory requirements.

6.1.1.2. Handling and Storage

The instructions for drug ordering are in the Pharmacy Binder. Pamiparib must be kept at 15-30°C. An accurate study drug accountability log must be maintained and kept up-to-date at all times.

6.1.1.3. Dosage and Administration

Pamiparib 60 mg will be administered PO BID, once in the morning and once in the evening, approximately 12 hours apart, each day for the protocol-prescribed dosing period. Pamiparib can be dosed with TMZ.

A lower dose of pamiparib or a QD regimen for pamiparib may be explored (see Section 4.2.1).

Patients will be instructed to swallow the capsules whole, in rapid succession, with water. Patients will be required to fast for at least 2 hours before and 1 hour 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 (first dose) and TMZ should be administered in the clinic.

6.1.2. Temozolomide

6.1.2.1. Packaging and Labelling

Capsules of TMZ are available in 5 mg, 20 mg, 100 mg, and 140 mg, depending on dose level and capsule availability. Please refer to the package insert for detailed information.

6.1.2.2. Handling and Storage

Please refer to the package insert for detailed information.

6.1.2.3. Dosage and Administration

Temozolomide will be administered PO QD, preferably in the morning (see dosing schedule below Table 2). TMZ can be administered with pamiparib. The daily dose and schedule will be determined as outlined in Section 4.2.1.

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

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.

In this study, TMZ will be administered as a flat dose rather than based on body surface area (BSA). The conversion of dose levels for TMZ for this study into BSA-based doses are as follows in Table 2.

Table 2: Comparison of Temozolomide Dosing: Flat fixed versus BSA-based

Flat Dose QD	BSA Equivalent[1]
20 mg	11.5 mg/m^2
40 mg	23.0 mg/m^2
60 mg	34.7 mg/m^2
80 mg	46.0 mg/m^2
120 mg	69.0 mg/m^2

BSA = body surface area; QD = once daily
[1] Dose equivalent information is provided for reference only and assumes an average body surface area of 1.73 m^2

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

6.1.2.4. 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 TMZ 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 TMZ and MTIC (USPI).

A CYP phenotyping study using human liver microsomes with selective CYP inhibitors and recombinant CYP enzymes suggests that CYP3A is the major CYP isoform responsible for pamiparib metabolism while CYP2C8 contributes 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 refer to the IB for additional information [59].

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

6.1.3. Modifications of Study Drugs

6.1.3.1. General Considerations for Modifications of Study Drugs

AEs should be assessed as best as possible regarding their relatedness to one or both study drug(s). Investigators should discuss potential dose modifications with the Medical Monitor prior to implementation, if feasible. Regardless of discontinuation of one or both study drugs, patients should continue on study, with regular follow-up as outlined in Section 8.5.

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 drug(s) after the DLT assessment window, may temporarily suspend study drug. Depending on the toxicity, study drug 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 without discontinuing the patient from the study. If study drug is planned to be held > 28 days, the medical monitor must be contacted before permanent patient discontinuation.

Criteria for dose 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.

6.1.3.2. Dose Interruption and Modification of Pamiparib and Temozolomide

As discussed in Section 1.3 and Section 1.6, PARP inhibitors show at least partial overlap with the safety profile of TMZ, thus making it likely that patients in this study may experience pamiparib and TMZ-related AEs 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.

In the context of this study, the role of TMZ is to sensitize tumor cells to pamiparib through DNA damage that can be caused by relatively low doses of TMZ. Given the favorable safety profile of pamiparib (Section 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 two TMZ dose reductions are allowed.

Patients enrolled in the pulsed schedule (Arm A) who undergo AEs may re-start TMZ after the AE has recovered at the same dose or at a reduced dose as specified in Table 3, provided 3 weeks have passed from the last full TMZ dosing. For alternate scenarios, please contact the medical monitor for instructions. Pamiparib should be resumed and administered continuously at 60 mg BID, unless a dose reduction is specified.

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 two 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 may be discussed with the Medical Monitor. If the blood count levels have not recovered to NCI-CTCAE Grade 1 or less after 4 weeks, further investigations should be

considered, including bone marrow analysis and blood sample for cytogenetics. If MDS or AML is confirmed, discontinue pamiparib. The criteria for dose modifications and reductions for pamiparib and TMZ are outlined in Table 3.

Table 3: Criteria for Interruption and Modification of Pamiparib and Temozolomide Dosing

Worst toxicity CTCAE 4.03 Grade (value)	**Recommended dose modification any time during a cycle of therapy**
Hematologic	
Anemia (hemoglobin, Hgb)	
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)	• **Subsequent occurrence following dose reduction for anemia:** • Continue pamiparib and TMZ without interruption with appropriate supportive care based on clinical assessment OR • Hold pamiparib and TMZ and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR • Hold pamiparib andTMZ and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ TMZ by 1 additional dose level
Grade 4 (life threatening consequences; urgent intervention indicated)	• **Second occurrence following dose reduction for anemia:** • Hold pamiparib and TMZ and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ TMZ by 1 additional dose level • **Third occurrence following 2 dose reductions for anemia:** • Discontinue pamiparib and TMZ if anemia is not caused by any other confounding event, e.g., gastrointestinal hemorrhage • Hold pamiparib and TMZ and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level
Neutropenia (ANC)	
Grade 3 (ANC < 1.0 - 0.5 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 (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

Table 3: Criteria for Interruption and Modification of Pamiparib and Temozolomide Dosing (Continued)

Worst toxicity CTCAE 4.03 Grade (value)	**Recommended dose modification any time during a cycle of therapy**
Thrombocytopenia	
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
Renal	
Serum Creatinine	
2-3 x ULN	Hold BGB-290 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 ↓ pamiparib and 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 (e.g. review of peripheral blood smear and haptoglobin determination), then ↓ pamiparib and TMZ by 1 dose level and continue study drug administration at the discretion of the investigator.
AST 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, discontinue pamiparib and TMZ • If persistent for > 14 days, discontinue pamiparib and TMZ
Grade 4 (> 20 x ULN)	Permanently discontinue pamiparib and TMZ
Pancreatic	
Pancreatitis Grade 3 or 4	Permanently discontinue pamiparib and TMZ

Table 3: Criteria for Interruption and Modification of Pamiparib and Temozolomide Dosing (Continued)

Worst toxicity **CTCAE 4.03 Grade (value)**	**Recommended dose modification any time during a cycle of therapy**
Cardiac	
Cardiac - prolonged QTc interval QTcF > 500 ms or > 60 ms from the highest value at baseline or predose	• Obtain triplicate ECGs (5 minutes apart) ~1 hour after initial ECG • If mean QTcF > 500 ms, hold pamiparib and TMZ until evaluation of ECGs by cardiologist a. Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF > 500 ms confirmed by cardiologist, 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

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECG = electrocardiogram; Hgb = hemoglobin; ms = milliseconds; PLT = platelet; QTc = QT interval corrected for heart rate; QTcF = QT interval corrected for heart rate using Fridericia's formula; TMZ = temozolomide; ULN = upper limit normal

6.1.4. Product Accountability

The investigator 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.

After completion of the study, all unused pamiparib will be inventoried and packaged for return shipment. 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.

6.1.5. Assessment of Treatment Compliance

On all visits to the study center, patients will be questioned in regard to compliance with study instructions.

6.1.6. Treatment of Overdose from Study Drugs

Overdose is defined as a patient having taken (accidentally or intentionally) a dose of pamiparib or TMZ that exceeded the dose assigned per protocol by ≥ 20%. 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 as a result of an overdose should be reported to the Medical Monitor as well as being included in standard AE reporting.

6.1.7. Occupational Safety

Pamiparib is not expected to pose significant occupational safety risks 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.

6.2. Concomitant Medications and Non-Drug Therapies

6.2.1. Permitted Medications

All treatments and supportive care, including 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 electronic case report form (eCRF) including all prescription and over-the-counter (OTC) drugs, herbal supplements, and intravenous (IV) medications and fluids. If changes occur during the study period, documentation of changes in drug dosage, frequency, route, and date will also be included on the eCRF.

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 drug 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.

6.2.2. Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including surgery, radiation therapy (RT), and cytotoxic, biologic, investigational agent, anticancer Chinese medicine, or hormone therapy. Bisphosphonate and denosumab use are permitted if the patient had already been receiving it at a stable dose ≥ 28 days prior to Day 1. Palliative treatment of isolated lesions (except target lesions) with local radiation therapy is allowed.

The primary metabolic pathway for pamiparib involves the CYP3A isoform, thus co-administration of strong/moderate inhibitors of CYP3A with pamiparib should be avoided. Also avoid strong CYP3A inducers with pamiparib. Please refer to the drugs/substances presented in Appendix 4 and to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list of medications that should be avoided.

Avoid the use of drugs that are known to cause prolongation in QT/QTc interval and/or induce Torsades des Pointes. Please refer to Appendix 6 for a list of these drugs. If the use of any of these drugs is necessary, the Medical Monitor should be contacted.

Avoid valproic acid as it decreases oral clearance of temozolomide (see package insert for temozolomide).

Grapefruit juice is not allowed throughout the study. No other dietary restrictions will apply.

6.2.3. Medications to Be Used with Caution

Based on preliminary *in vitro* screening assays, pamiparib is not a strong inhibitor of other human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Investigators need to be aware that pamiparib has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C9 and follow the prescribing information recommendations for use with CYP2C9 inhibitors. Therefore, 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.

7. STUDY PROCEDURES

7.1. Informed Consent

All patients will provide their written informed consent before the performance of any study related procedures.

A separate informed consent (Section 8.1) must be signed by patients who undergo collection of blood and/or biopsy to provide fresh tumor tissue sample for HRD/*BRCA* mutation central laboratory testing during prescreening.

During the informed consent process, male patients 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.

7.2. Patient Demographics and Other Baseline Characteristics

7.2.1. Demography

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

7.2.2. Medical History

The medical history and prior medications assessments are the same for both the dose escalation and dose expansion phases of the study.

Clinically significant medical history findings (e.g., previous diagnoses, diseases, or surgeries) not pertaining to the study indication, which started before the patient signed the informed consent, and were 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 requiring treatment, 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.

7.2.3. Cancer Characteristics

The following information will be collected: the date and stage of initial cancer diagnosis, anatomic site of metastases, all prior anticancer therapies including surgery, radiation therapy, and systemic treatments with dates administered. Start dates, stop dates, best response, and reasons for treatment discontinuation will be collected.

Patients with ovarian cancer are defined as platinum-sensitive if disease progression by RECIST v1.1 or GCIG CA-125 criteria had occurred more than 6 months after their last platinum chemotherapy. Ovarian cancer patients are defined as platinum-resistant if disease progression occurred less than 6 months after their last platinum chemotherapy but after their post-treatment evaluation, and as platinum-refractory if they experienced disease progression while receiving platinum chemotherapy, up to the date of their post-treatment evaluation.

7.2.4. Other Baseline Parameters

Information will also be collected regarding prior medications/significant non-drug therapies, smoking history, childbearing potential (Appendix 2) and any other assessments that are done for the purpose of eligibility for inclusion into the study (physical examination, vital signs, complete blood count [CBC] and blood chemistry, urinalysis, pregnancy test, and ECG). For further details on eligibility assessments, please see Section 5 and Appendix 1.

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

A complete or limited physical examination, vital signs (systolic and diastolic blood pressure [SBP and DBP, respectively], pulse rate, oral, temporal, or tympanic temperature, and respiratory rate), weight, height (Screening only) and ECOG performance status will be performed at timepoints specified in Appendix 1.

A complete physical examination should include an evaluation of general appearance as well as 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 be directed at the evaluation of symptoms or specific safety issues. New or worsening abnormalities should be recorded as AEs if appropriate.

ECOG performance status will be determined as outlined in Appendix 8.

7.4. Adverse Events

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

SAEs, regardless of the relationship to the study drug, will be collected from the time of patient informed consent. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study treatment or initiation of new anticancer therapy. All treatment-related AEs and SAEs will be followed until resolution or stabilization. The accepted regulatory definition of AEs and important additional requirements for SAE reporting are outlined in Section 10.

7.5. Electrocardiogram

During screening, a single 12-lead ECG with assessment of PR interval, QRS duration, and QTc interval will be obtained within 14 days of Cycle 1 Day1. The screening ECG will be read locally to determine eligibility.

Dose Escalation and Expansion Cohorts 1-5 ONLY

During Cycle 1 and the pamiparib PK intensive period (Day -2), ECGs will be performed in triplicate on a machine provided by the sponsor within a 5-minute window **prior** to pamiparib PK assessments (see below and Section 7.8) at the timepoints indicated below:

- Pre-dose (within 30 min prior to dose)
- Post-dose:

- 1 hour (± 15 min)
- 2 hours (± 30 min)
- 4 hours (± 30 min)
- 6 hours (±30 min)

ECGs for each patient should be obtained from the same machine whenever possible. Central read of ECGs obtained during the PK assessments will be performed for dose escalation and dose expansion cohorts 1-5.

Locally obtained ECGs should be performed if clinically indicated for all patients enrolled in the study. To minimize postural variability, it is important that patients are resting and in a 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.

7.6. Laboratory Studies

Samples for a complete blood count (CBC), chemistry, and coagulation profiles will be drawn and analyzed locally. All other required blood samples will be sent to 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 materials, such as test tubes and labels, is provided in the Study Manual.

Laboratory studies will be performed at the timepoints specified in Appendix 1 (including allowed windows of assessment) and may also be performed as medically necessary. Laboratory assessments should be done before study drug administration.

Screening blood and urine tests must be performed within 14 days of Day 1. If they were performed within 4 days of Day 1, they do not need to be repeated on Cycle 1 Day 1.

7.6.1. Hematology Studies

A CBC includes hemoglobin, hematocrit, platelet count, red blood cell (RBC) count and white blood cell (WBC) count with differential.

7.6.2. Clinical Chemistry

Chemistry includes albumin, alkaline phosphatase (ALP), AST, ALT, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactic acid dehydrogenase (LDH), phosphate, potassium, sodium, total bilirubin, and total protein.

7.6.3. Coagulation

The coagulation profile includes international normalized ratio (INR) and activated partial thromboplastin time (aPTT), to be performed only at screening and as clinically indicated.

7.6.4. Hepatitis B and C Testing

Hepatitis B and C testing will be performed by a local laboratory at screening and as clinically indicated and will include HBV/hepatitis C virus (HCV) serology (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).

7.6.5. Urinalysis with Dipstick

Urinalysis will be assessed using urine dipstick. Urine microscopy will be performed if urine dipstick is abnormal. Urinalysis includes pH, glucose, protein, ketones, bilirubin, blood, and specific gravity. If urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and a random urine for total protein and creatinine will be performed at screening only or as clinically indicated. All tests will be performed in local laboratories.

7.6.6. Pregnancy Test

Clinical Trial Facilitation Group (CTFG) recommendations related to contraception and pregnancy testing in clinical studies include for females with childbearing potential the use of highly effective forms of birth control (Appendix 2) and testing for pregnancy every 28 days. During screening, a serum pregnancy test must be obtained ≤ 7 days prior to Day 1. For subsequent pregnancy testing on study and at EOT, urine pregnancy tests are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.

7.6.7. CA-125 Measurements

CA-125 levels will be collected for ovarian cancer patients and tested in a certified local laboratory during screening and every 8 weeks (± 7 days) following the first administration of the investigational medical product (Appendix 1).

Increases and decreases in CA-125 levels will be tracked in order to assess CA-125 responses by the GCIG criteria described in Appendix 9.

7.6.8. PSA Measurements

PSA levels will be collected for prostate cancer patients and tested in a certified local laboratory during screening and every 8 weeks (±7 days) following the first administration of the investigational medical product (Appendix 1). In addition, the three most recent PSA levels prior to screening will need to be provided to determine a baseline doubling time.

Increases and decreases in PSA will be tracked in order to assess PSA responses by the PCWG2 criteria described in Appendix 10. PSA changes from baseline (either increment or decline) and maximal change in PSA will be recorded and responses assigned by PCWG2 criteria. PSA responses and progression must be confirmed 28 days later.

Although serial PSA will be measured in this study and PSA progression documented by the PCWG2 criteria, the PSA value on its own is not considered a reliable measure of clinical benefit and does not correlate tightly with survival. PSA flares may occur early in the study drug administration and may therefore confound response assessment. Additionally, there is emerging data that PARP-1 is implicated in multiple other essential cellular functions separate from DNA repair including ETS gene-mediated transcription regulation which may have a bearing on the

response assessments by PSA. PSA reading should not be applied as the sole criteria to consider discontinuation of study drugs. In absence of evidence of radiological or clinical evidence of disease progression, patients with mCRPC should continue in the study despite an increment in PSA. Therefore, patients will not be taken off study purely for rising PSA levels in the absence of worsening scans and symptoms since PARP inhibitors may impact tumor growth without impacting PSA secretion. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG2 criteria (Appendix 10).

7.7. Tumor Assessment

Tumor imaging (CT or MRI, with preference for CT) will be performed at screening and every 8 weeks (±7 days) from Cycle 1 Day 1 until disease progression. Any evaluable disease must be documented at screening and reassessed at each subsequent tumor evaluation. At the investigator's discretion, CT scans may be repeated at any time if progressive disease is suspected. An objective response is considered confirmed once repeat assessments ≥ 4 weeks after initial documentation are available.

A CT scan or MRI of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate, including bone scan for patients with bone metastasis, will be performed to assess all known disease. All known disease must be documented at baseline as target or non-target lesions using RECIST v1.1. The CT scan will be used for the evaluation criteria RECIST v1.1 by the investigator at each study center. Routine use of positron emission tomography (PET) scans should not be used to assess radiologic response to treatment for this study.

Unless contraindicated, intravenous contrast product must be used to maximize visualization of all lesions. Patients who are at increased risk of allergic reaction to iodinated contrast media should not have enhanced CT, but should instead be provided magnetic resonance imaging (MRI) with gadolinium enhancement patient per local protocol, with mandatory imaging coverage from thoracic inlet to symphysis pubis plus unenhanced CT scanning with coverage from the thoracic inlet to the inferior costophrenic recess. Patients with bone pain or biochemical changes suggestive of bony disease without other clear explanation should have a bone scan at baseline and if bone metastases are documented should then have bone scans or other appropriate imaging examinations as clinically indicated.

The same imaging technique should be used on the same patient throughout the study.

After first documentation of response (CR or PR), imaging performed at the next regularly scheduled timepoint may be used for response confirmation.

Patients who permanently discontinue study drugs prior to progressive disease will continue with regular tumor assessments as per protocol every 8 weeks (±7 days) until disease progression, administrative issues, start of other anticancer therapy or any other reason listed in Section 8.4, whichever occurs first. This imaging schedule will be maintained regardless of any intermediate unscheduled scans. Patients who withdraw from the study for clinical or symptomatic deterioration before objective documentation of progressive disease will be requested to undergo appropriate imaging to confirm progressive disease. Every effort will be made to confirm a clinical diagnosis of progressive disease by imaging.

All efforts will be made to ensure that the imaging equipment, contrast agent, and person (investigator or radiologist) performing the evaluation is kept constant throughout a patient's course on study.

7.8. Pharmacokinetics of Pamiparib and Temozolomide

Blood will be collected to characterize the PK of both pamiparib and temozolomide. Additionally, blood may also be used to explore the presence of metabolites in a qualitative or semi-quantitative manner.

Blood sampling for PK will be collected at the timepoints specified in Schedule of Assessments (Appendix 1 Table 1).

Details concerning handling of the PK plasma samples, including labeling and shipping instructions will be provided in the Study Manual.

Samples will be shipped to the central laboratory where they will be stored and batch shipped to the designated bioanalytical laboratory for quantification of plasma pamparib and TMZ concentrations using a validated method.

7.8.1. PK of Pamiparib

To better characterize the pamiparib PK profile prior to TMZ administration, the first 15 patients enrolled into the study in dose escalation will undergo intensive PK sampling starting on Day -2 at the following timepoints: pre-dose (within 30 min prior to dose), 30 minutes (± 5 min), 1 hour (± 15 min), 2 hours (± 30 min), 4 hours (± 30 min), 6 hours (± 30 min); 24 hours (± 2 hours) post-dose on Day -1; and 48 hours (± 2 hours) post-dose on Day 1 as detailed in Table 2 of Appendix 1.

After 15 patients have completed intensive PK sampling, all other patients enrolled in dose escalation and expansion will have PK samples collected at the following timepoints: pre-dose (within 30 min prior to dose), 1 hour (± 15 min), 2 hours (± 30 min), and 4 hours (± 30 min) post dose on both Cycle 1 Day 1 and Cycle 1 Day 15. The time of study drug administration on the day prior to Cycle 1 Day 15 must be recorded on the eCRF. Details concerning collection and handling of the PK plasma samples will be provided in the Study Manual.

7.8.2. PK of TMZ

Pharmacokinetic samples will be collected from patients in all cohorts at the following timepoints: pre-dose (within 30 min prior to dose) and 1 hour (± 15 min) post dose on Cycle 1 Day 1 and Cycle 1 Day 7. The time of study drug administration on the day prior to Cycle 1 Day 7 must be recorded on the eCRF.

7.9. Biomarker Assessments

The biomarker analysis includes but it is not limited to germline *BRCA1/2* mutation, HRD status, and somatic mutation analysis. Blood and biopsies for biomarker analysis will be collected at the timepoints specified in Schedule of Assessments (Appendix 1 Table 1).

7.9.1. Blood for biomarker analysis

All patients will provide blood samples for analysis of baseline germline *BRCA* and/or other mutations.

All patients will also provide blood samples to be processed into serum, plasma, and cell fractions for the analysis of germline mutations, and circulating markers, such as, but not limited to, circulating nucleic acids (CNA).

7.9.2. Tumor tissues for biomarker analysis

Patients from Dose Escalation, patients from Dose Expansion Cohorts 1-3 with known HRD or BRCA mutation status and patients from Dose Expansion Cohorts 4 and 5

An archived, formalin-fixed, paraffin-embedded tumor sample will be collected from all patients, if available, for retrospective analysis of HRD mutational status. Archival tumor tissue shall be sent to the central laboratory for biomarker testing (either a formalin-fixed, paraffin-embedded block with tumor tissue [preferred] or approximately 10 unstained slides). The most recent tumor block is preferred.

In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is highly recommended. Written patient consent is required for fresh tumor biopsies.

An optional biopsy will also be taken at the EOT visit for the patients who have confirmed disease progression from accessible tumor sites. These samples will be used to explore resistance mechanism(s). If feasible, any follow up biopsy should be from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies.

Fresh biopsies should be limited to readily accessible tumor lesions (e.g., skin, peripheral lymph nodes, lung, liver, or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis.

Patients from Dose Expansion Cohorts 1-3 with unknown BRCA 1/2 mutation or HRD status and Cohort 6

All patients who are potential candidates for enrollment on these cohorts must provide a mandatory archival tumor tissue sample (either a formalin-fixed, paraffin-embedded block with tumor tissue [preferred] or approximately 10 unstained slides) for central prospective testing of HRD status in order to determine their eligibility. The most recent tumor block is preferred. If no archival tumor tissue is available, a mandatory fresh tumor biopsy should be performed. Written patient informed consent is required for archival tissue or biopsy collection (prescreening informed consent).

Any tissues taken during pre-screening period will not be re-collected at screening or Cycle 1 Day 1.

7.9.3. Optional tumor biopsy for pharmacodynamics analysis (Dose Escalation and Dose Expansion Cohorts 1-5)

An optional biopsy for pharmacodynamics at Cycle 1 Day 1 and Cycle 1 Day 15 is highly recommended. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy.

Instructions for the processing, storage, and shipping of samples will be provided in the Study Manual.

7.10. Appropriateness of Measurements

All safety, PK, and tumor assessments used in this study are standard, i.e., widely used and generally recognized as reliable, accurate, and relevant. PK and PD assays will be performed using validated GLP methods.

8. STUDY VISITS AND FOLLOW-UP

8.1. Prescreening (Dose Expansion Only, Days -84 to -29 prior to Screening)

During the dose expansion phase of the study, patients in the Expansion Cohorts 1 to 3 (ovarian, TNBC, and mCRPC, respectively; see Section 5.1) who have unknown biomarker status will undergo pre-screening for evaluation of HRD status. All patients in the Dose Expansion Cohort 6 will undergo prescreening for central evaluation of HRD status. A separate pre-screening informed consent must be obtained.

An archival tumor sample is acceptable; however, if not available, a fresh tumor biopsy must be obtained for HRD testing.

The following will be performed during the pre-screening visit:

- Obtain written informed consent from the patient to perform a tumor biopsy if it is required for the purpose of meeting the eligibility of the study
- Prepare tumor samples and ship to the qualified central lab for mutation analysis as specified in the Study Manual

8.2. Screening Period (Day -28 to Day -1)

A signed, written informed consent must be obtained prior to screening assessments and before any study-specific assessments are initiated. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the screening windows may be used and do not need to be repeated as long as they meet protocol specifications. The study-specific assessments and procedures are shown in the Schedule of Assessments in Appendix 1 Table 1.

Screening Period assessments are the same for the dose escalation and dose expansion phases of the study and will be completed within 28 days prior to the first dose of the investigational product. Some assessments have a narrower screening window as shown in the Schedule of Assessments in Appendix 1 Table 1. Screening assessments obtained within 4 days of Day 1 do not have to be repeated on Day 1.

8.3. Assessments during Treatment Period

Safety assessments should be performed at all visits to the study center and throughout the study.

8.3.1. PK Intensive Visit (Day -2 to Day 1) (Dose Escalation Cohort ONLY)

To better characterize the pamiparib PK profile prior to TMZ administration, the first approximately 20 patients enrolled into the study will undergo intensive PK sampling starting on Day -2 as detailed in Appendix 1 Table 2.

Once 20 patients have completed the pamiparib PK intensive sampling, the remainder of patients will undergo limited PK sampling as detailed in Appendix 1 Table 1. Any modifications to assignment of PK sampling schedule may be implemented following discussion with the Medical Monitor.

Patients who participate in the PK intensive sampling will have baseline assessments performed on Day -2 before pamiparib dosing rather than on Day 1 as detailed in Appendix 1 Table 2.

Note: The collection of blood for the pamiparib PK 48-hour post-dose timepoint must occur **prior** to the administration of pamiparib and TMZ on Day 1.

8.3.2. Cycle 1 (28 days)

During Cycle 1, all assessments (except for PK post-dose blood collection) performed during the clinic visit must be done **prior** to study drug administration. On days with PK assessments, pamiparib (first dose) and TMZ should be administered in the clinic.

For the Dose Expansion Cohorts, a 2-day window is allowed during Cycle 1 visits.

A list of all of the activities during Cycle 1 is found in the Schedule of Assessments Table (Appendix 1 Table 1).

8.3.3. Subsequent Cycles

A list of all of the activities during subsequent cycles in the first year are listed in the Schedule of Assessments Table (Appendix 1 Table 1).

All assessments performed during the clinic visits and subsequent cycles must be done **prior** to study drug administration (unless otherwise noted).

8.3.4. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; and hematology and clinical chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected PD, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

8.4. End-of-Treatment Visit

Patients who discontinue from study drug for any of the reasons listed below will undergo an EOT visit within 7 days of discontinuation of all study drugs. If routine laboratory tests (e.g., hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated.

However, the EOT visit may occur later than 7 days after discussion with the Medical Monitor for specific circumstances, such as prolonged hospitalization. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of pamiparib and TMZ, the EOT Visit may also be used as the Safety Follow-up Visit.

Patients with a required EOT visit may discontinue study drug for any of the following reasons:

- Disease progression

- Investigator decision
- Adverse event(s)
- Pregnancy
- Patient withdrew consent for study drug
  - Patients may voluntarily withdraw consent from study drug at any time
  - Patients may continue to participate in the Follow-up Phase, if the patient withdraws consent from the Treatment Phase
- Start of other anticancer therapy
- Patient noncompliance
  Study site staff should first counsel patients who are significantly noncompliant (e.g., missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant

The reason for discontinuation from study drug will be recorded on the eCRF.

All the assessments performed for the EOT visit are listed in the Schedule of Assessments (Appendix 1 Table 1).

The visit at which the assessment showed progressive disease may be used as the EOT visit provided that all required assessments were performed. A CT does not have to be repeated at the EOT visit if it was performed within 14 days of the visit or at a prior response evaluation that documented progressive disease. ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

8.5. Follow-up Assessments

8.5.1. Safety Follow-Up

All patients who discontinue study drugs will have a safety follow-up approximately 30 days after the last day of study drugs to collect AEs and SAEs that may have occurred after the patient discontinued from the study drugs as well as concomitant medications. The investigator or his/her designee will also contact the patient to collect AE and SAE information as well as any new anticancer therapy given after the last day of study drugs. A laboratory assessment is only required if the patient had an ongoing laboratory abnormality at the previous visit that the investigator considered to be related to study drugs.

8.5.2. Efficacy Follow-Up

Patients who were not discontinued from study drugs due to disease progression and meet criteria otherwise (e.g., 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 8.4, whichever occurs first.

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.

8.5.3. Survival Follow-Up

Patients enrolled during the dose expansion phase of the study will be followed for survival and further anticancer therapy information post progression via phone contact (with the patient's guardian, if applicable) or other means (e.g., clinic visit or review of medical records) approximately every 3 months (Appendix 1 Table 1).

8.5.4. Lost to Follow-Up

If attempts to contact the patient by telephone are unsuccessful, additional attempts should be made to obtain protocol-required follow-up information. It may be possible to obtain the information from other contacts, 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.

8.6. End of Study for Individual Patients

Patients who end participation in the study do not contribute additional data at any subsequent visits (including the EOT and all follow-up visits). Patients who end participation in the study may do so under the following circumstances:

- Patient withdrew consent for study participation
  - Patients may voluntarily withdraw consent from the study at any time.
- Lost to follow-up
- Death
- Study termination by sponsor
- Other, as per the discretion of the sponsor or health authority

The reason for discontinuation from study participation will be recorded on the eCRF.

8.7. End of Study

The end of study is defined as the timepoint when the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, or is lost to follow up. Alternatively, the end of study is when the sponsor decides to terminate the study.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients must be seen for an EOT Visit and Safety Follow-up Visit as described in Section 8.4 and Section 8.5.1.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

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. Site audits may be made periodically by the sponsor's or the contract research organization's (CRO'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 required by the protocol will be entered into the eCRFs in an electronic data capture (EDC) system that is compliant with all regulatory requirements or transmitted to BeiGene by third party vendors, as applicable.

Data collection in the eCRF must follow the instructions described in the eCRF Completion Guidelines (eCCGs). The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Form FDA 1572 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 (e.g., 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 site 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®). Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant diseases/medical history will be coded using the MedDRA®.

9.3. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct quality assurance audits. 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 (e.g., 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 prior to submission to the sponsor.

10.1.1.1. 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 v4.03.

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 (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated, disabling, limiting self-care ADL
- 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 (for example, 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.

10.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drugs and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, 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 Pamiparib Investigator’s Brochure [59] 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 makes assessment of causality for every SAE prior to 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 “a reasonable possibility” that the AE may have been caused by the study drug (i.e., there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

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

An AE should be considered ‘related’ to study drug if any of the following are met:

- 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 (e.g., 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 (e.g., the patient’s clinical condition or other concomitant AEs).

An AE should be considered ‘unrelated’ to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the study drug and the onset of the AE (e.g., the AE occurred either before or too long after administration of the product for it to be considered product-related)
- A causal relationship between the study drug and the AE is biologically implausible (e.g., death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related AE)

10.1.1.3. Follow-Up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

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 or SAE 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 post-mortem findings, including histopathology.

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

10.1.1.4. Laboratory Test Abnormalities

Abnormal laboratory findings (e.g., clinical chemistry, CBC, coagulation, or urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE (as defined in Section 10.1.1) or an SAE (as defined in Section 10.2).

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be

reported as AEs or SAEs. They should only be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, require dose interruption or discontinuation or are clinically significant in the opinion of the investigator.

The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

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 (e.g., 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 (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

10.3. Definition of a Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (i.e., not present in the study drug's reference safety information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the Pamiparib Investigator's Brochure. [59]

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

10.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study treatment or initiation of new anticancer therapy.

After a patient is discontinued from the study, investigators are not obligated to actively seek AEs or SAEs from the former patients. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

10.4.2. 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?

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

10.5.1. Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (e.g., record only hepatitis rather than elevated transaminases, bilirubin, or jaundice). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual

signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

10.5.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (e.g., clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report, if applicable). However, if a patient initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

10.5.3. Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, it should be recorded as a new AE on the eCRF (and a stop date should be recorded in the previous AE).

A recurrent AE is one that occurs and resolves between patient evaluation timepoints, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

10.5.4. Disease Progression

Disease progression is measured as an efficacy endpoint and is not considered to be an AE. However, if there are separate identifiable clinical sequelae that result from disease progression, those sequelae are reportable as AEs. For instance, a patient with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as “pleural effusion” instead of disease progression or metastasis to lungs. If a patient has a seizure that is determined to be associated with a brain metastasis, the term “seizure” should be recorded as the AE instead of disease progression or brain metastasis. If a patient experienced multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data. They should not be reported as an SAE. If deaths are assessed by the investigator as not solely due to disease progression, whether they are assessed as related or not related to the study drug, they should be reported as SAE immediately.

If there is any uncertainty regarding whether an AE is due to disease progression, it should be reported as an AE.

10.5.5. Death

Death is an outcome, not an event. If an AE/SAE results in death, then the term of the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “unexplained death”.

10.6. Prompt Reporting of Serious Adverse Events

10.6.1. Timeframes for Submitting Serious Adverse Events

Serious adverse events will be reported promptly (within 24 hours) to the sponsor or designee as described in Table 4 and the Study Manual once the investigator determines that the AE meets the protocol definition of an SAE.

Table 4: Time Frame for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial SAE Report	Documentation	Timeframe for sending follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE report form

SAE, serious adverse event.

10.6.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined 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 timeframes.

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 will always provide an assessment of causality at the time of the initial report as described in Section 10.1.1.2.The sponsor will provide contact information for SAE receipt.

10.6.3. 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. 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.

All suspected unexpected serious adverse reactions will be submitted to all applicable regulatory authorities and investigators for pamiparib studies.

When a study center receives an initial or follow-up safety report or other safety information (e.g., revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of Safety Reports from the sponsor in the Investigator Site File.

10.7. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy 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. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. 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 always be 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.

10.8. 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 following reference documents:

- Pamiparib (BGB-290) Investigator's Brochure [59]

11. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released. 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

For the dose escalation phase, data will be summarized by dose level. For the dose expansion phase, data will be summarized by cohort.

Descriptive statistics will be mainly used in describing the anticancer activities and tolerability of the pamiparib and TMZ combination regimens. Confidence intervals will be constructed to describe the precision of the point estimates of interest (e.g. objective response rate and disease control rate).

11.2.1. Analysis Populations

Safety Population includes all patients who received any dose of pamiparib and/or TMZ. The Safety Population will be used for all safety analyses.

Efficacy Evaluable Population includes patients in the Safety Population who had measurable disease (or evaluable disease for patients enrolled into the dose escalation phase) at baseline (or prostate cancer patients as per inclusion criterion 14f) and had at least one post-baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

DLT Evaluable Population includes patients who received ≥ 70% of each study drug during the DLT assessment window and had sufficient safety evaluation. Additionally, patients who had a DLT event during the DLT assessment window despite receiving < 70% of the scheduled dose will also be considered evaluable.

PK Population includes all patients for whom valid pamiparib PK parameters can be estimated.

11.2.2. Patient Disposition

The number of patients enrolled, treated, discontinued from study drug, and those with major protocol deviations will be counted by cohort. 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

Demographic and other baseline characteristics will be summarized by cohort in the Safety Population using descriptive statistics. Continuous variables include age, weight, vital signs, time

since initial tumor diagnosis, time since metastatic disease; categorical variables include sex, age group (< 65 versus ≥ 65 years), race, disease stage, ECOG-PS, prior line of therapy in the metastatic setting, and geographic region.

11.2.4. Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the WHO-DD drug 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 stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose. A listing of prior and concomitant medications will be included in the CSR of this protocol.

11.2.5. Efficacy Analyses

No formal hypothesis testing is planned in this Phase 1b study.

For solid tumors other than prostate cancer, tumor assessment based on investigator assessment according to RECIST v1.1 will be used to calculate ORR, DCR, PFS, and DOR, as well as timepoint estimate PFS-6m. Overall survival (OS) and OS-6m will be summarized as well. For patients with ovarian cancer, tumor response may also be assessed by investigators based on GCIG criteria which use carcinoma antigen-125 (CA-125) in combination with RECIST v1.1 (Appendix 9).

For patients with prostate cancer, PSA and tumor lesions will be evaluated together to determine the tumor response according to PCWG2 criteria (Appendix 10).

ORR is defined as the proportion of patients who have a best overall response (BOR) of CR or PR, where BOR is defined as the best response recorded from the first dose of study drugs until data cut, disease progression, or start of new anti-neoplastic treatment. Binomial exact 90% and 95% confidence intervals will be calculated for ORR in each cohort.

DCR is defined as the proportion of patients with BOR of CR, PR, and SD. It will be summarized similarly as ORR.

PFS is defined as the time from the date of the first dose of study drugs 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 imaging and laboratory assessments, if possible, to correlate radiographic findings with the clinical findings. Data for patients without disease progression or death by the time of analysis will be censored at the time of the last tumor assessment. Data from patients who are lost to follow-up prior to documented disease progression will be censored at the last tumor assessment date when the patient is known to be progression-free. 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 the first dose of study drugs to death.

Time to event variables PFS, DOR, and OS will be estimated using the Kaplan-Meier (KM) method. KM estimates of PFS, DOR, and OS will be plotted over time. Median PFS, DOR, and OS, if estimable, in each cohort will be presented, along with their 2-sided 95% confidence intervals using a generalized Brookmeyer and Crowley method. The PFS-6m and OS-6m, defined as the percentages of patients in the analysis population who remain alive and progression free at 6 months (or alive at 6 months for OS-6m), will be estimated using the KM method along with the corresponding 95% confidence interval constructed using Greenwood's formula.

Maximum tumor shrinkage per patient will be presented in waterfall plots.

Primary analysis of efficacy endpoints will be carried out based on the maturity of the efficacy and safety data in the study, which will be determined by the sponsor.

ORR and DCR will be summarized in the specified subgroups: sex, age group (< 65 versus ≥ 65), race, disease stage, ECOG-PS (0 versus 1), number of prior lines of therapy, and geographic region.

11.2.6. Pharmacokinetic Analyses

For patients who contributed full PK profiles up to 48 hours on Cycle 1 Day 1, and up to 6 hours on Cycle 1 Day 15 (Section 8.3.1), the following PK parameters will be derived: C_{max}, T_{max}, $t_{1/2}$, apparent clearance of the drug from plasma (CL/F), and V_z/F.

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

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

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

11.2.7. Exploratory Analyses

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

11.3. Safety Analyses

Safety will be assessed by monitoring and recording of all AEs graded by NCI CTCAE v4.03. Laboratory values (CBC, clinical chemistry, coagulation, and urinalysis), vital, physical exams, and ECGs findings will also be used in determining the safety.

11.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized in each cohort descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose reductions, dose delay, and drug discontinuation due to AEs will be summarized by dose level. Frequency of dose reduction and dose delay 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 toxicity in the DLT evaluation period will be used to determine the dose and schedule of pamiparib plus TMZ in the expansion cohorts. The DLT events will be summarized descriptively at each combination dosing level in the DLT evaluable Population.

11.3.3. Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA®. Adverse events will be coded to MedDRA® (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA® preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment emergent adverse event (TEAE) is defined as an AE that had an onset date on or after the first dose of study drugs up to 30 days following study drug discontinuation or was worsening in severity from baseline (pretreatment). Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest grade according to NCI CTCAE v.4.03 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 drug. Treatment-related AEs include those events considered by the investigator to be possibly or probably related to study drug or with missing assessment of the causal relationship. Serious adverse events, deaths, TEAE with Grade 3 or above, related TEAE and TEAEs that led to treatment discontinuation, dose reduction or dose delay will be summarized.

11.3.4. Laboratory Analyses

Clinical laboratory (i.e., CBC, serum chemistry, and qualitative urinalysis) values will be evaluated for each laboratory parameter by cohort. Abnormal laboratory values will be flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the CSR for this protocol. Descriptive summary statistics (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst post-baseline visit.

Laboratory parameters that are graded in NCI CTCAE v.4.03 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, parameters with CTCAE grading in both high and low directions (e.g., calcium, glucose, magnesium, potassium, sodium) will be summarized separately.

11.3.5. Vital Signs

Descriptive statistics for vital sign parameters (SBP and DBP, heart rate, respiratory rate, temperature, weight) and changes from baseline will be presented by visit and cohort. Vital signs will be listed by patient and visit.

11.3.6. Electrocardiogram

Electrocardiogram assessments will be performed at Screening and during BGB-290 PK collection timepoints (Dose Escalation and Dose Expansion Cohorts 1-5) or at Screening, EOT and as clinically indicated (Cohort 6) as specified in the Schedule of Assessments (Appendix 1 Table 1). Change from baseline to each post-baseline visit in ECG findings will be summarized by visit and/or timepoint. Descriptive statistics for ECG parameters and changes from baseline will be presented.

11.4. Sample Size Consideration

Approximately 250 patients (50 in the dose escalation phase and 200 in the dose expansion phase) will be enrolled. A sample size of 20-25 patients in an expansion cohort will provide the half width of the 90% confidence interval of the ORR approximately 13% to 20% when the observed ORR is approximately 40%. Hence, the low bound is above 20%. This is considered adequate in the preliminary assessment of anticancer activity of pamiparib and TMZ combination therapy. An expansion cohort can be further expanded to confirm efficacy.

Table 5: Estimated Objective Response Rate and 90% Confidence Interval for 20-25 Patients

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

11.5. Interim Analysis

No interim analysis is planned.

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

This study will be conducted by the principal investigator and the study center in full conformance with the International Council for Harmonisation E6 guideline for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the International Council for Harmonisation E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

12.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted 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 informed consent form, and any other information that will be presented to potential patients (e.g., advertisements or information that supports or supplements the informed consent) 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 informed consent form, 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 informed consent form including obtaining IEC/IRB approval of the amended form before new patients consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/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 consent form for documenting written informed consent. Each informed consent 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 case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

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

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location. Patient medical information obtained during this study is confidential and may only be disclosed to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the United States Food and Drug Administration and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the IB, this protocol, eCRFs, the investigational new drug application, and any other study information, remain the sole and exclusive property of the sponsor 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 the sponsor. 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 is executed and includes confidentiality provisions inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

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 in the appropriate 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 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 at their specific study site on CD-ROMs for archiving the data at the study site.

12.2.7. Drug Accountability

The investigator or designee (i.e., 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 the sponsor and quantities dispensed to patients, 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 site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene's requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the sponsor's requirements for disposal, arrangements will be made between the site and the sponsor 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. Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed 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.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

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 ascertain 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.

12.2.10. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of the clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (i.e., last patient, last visit).

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 the sponsor. All protocol modifications must be submitted to the IRB/IEC together with, if applicable, a revised model informed consent in accordance with local requirements. Written documentation of IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in medical monitor or contact information).

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 informed consent form confirming willingness to remain in the study.

12.3.2. Use of Information and Publication

A clinical study report will be prepared and provided to the regulatory agency(ies) of participating countries. The sponsor 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 the 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 a multicenter study, 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).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor 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 study will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

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
- 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 samples (e.g., PK, biomarker, etc.) 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 significant non-compliance. 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 prior to 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, informed consent, 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 (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

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: archival at an off-site facility or transfer of ownership of 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, special arrangements must be made between the investigator and the sponsor to store these in sealed containers outside of the site so that they can be returned sealed 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 site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, a period of up to 10 years or as allowed by your IRB/IEC, whichever is shorter.

12.5.2. Provision of Study Results and Information to Investigators

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

In addition, details of the study drug assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

The sponsor will not routinely inform the investigator or patient the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

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 which 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 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.

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 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.

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 which may be published as described in Section 12.2.3

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 eCRFs 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 the sponsor 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 the sponsor access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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14. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Appendix 1 Table 1: Schedule of Assessments and Procedures Schedule for Dose Escalation and Dose Expansion Phases

Assessments	**Pre-Screening (Dose Expansion only)[1]**	**Screening[2]**	**Cycle 1 (28 days)**				**Cycles 2- 5 (28 days)**		**Cycle 6 and Subsequent Cycles in 1st year (Every 28 days)**	**Subsequent Cycles in the 2nd year and beyond (Every 28 days)**	**EOT[3]**	**Safety Follow-up[4]**	**Efficacy Follow-Up**	**Survival Follow-Up[5]**
Day of Phase	**-84 to -29**	**-28 to -1**	**1**	**7**	**15**	**22**	**1**	**15**	**1**	**1**	**~7 days after last dose**	**~30 ± 7 days after last dose**	**Every 8 weeks**	**Every ~3 months**
Allowed time window				**-2 days[6]**	**± 2 days**	**± 2 days**	**± 2 days[6]**	**± 2 days**	**± 3 days**	**± 3 days**			**±7 days**	
Pre-screening informed consent	X													
Informed consent		X												
Baseline demographics		X												
Medical and cancer history		X												
Complete Physical examination[7]		X									X			
Limited physical examination[8]			X	X	X	X	X	X	X	X				
Vital signs (including weight)		X	X	X	X	X	X	X	X	X	X			
Height		X												
ECOG performance status		X	X				X		X	X	X			
12-lead ECG[9]		-14 to -1 X									X			
Triplicate ECGs[10]			X		X									
Hematology[11]		-14 to -1 days X[12]	X	X	X	X	X	X	X	X	X			
Clinical chemistry[11]		-14 to -1 X[12]	X	X	X	X	X	X	X	X	X			

Assessments	**Pre-Screening (Dose Expansion only)[1]**	**Screening[2]**	**Cycle 1 (28 days)**				**Cycles 2- 5 (28 days)**		**Cycle 6 and Subsequent Cycles in 1st year (Every 28 days)**	**Subsequent Cycles in the 2nd year and beyond (Every 28 days)**	**EOT[3]**	**Safety Follow-up[4]**	**Efficacy Follow-Up**	**Survival Follow-Up[5]**
Day of Phase	**-84 to -29**	**-28 to -1**	**1**	**7**	**15**	**22**	**1**	**15**	**1**	**1**	**~7 days after last dose**	**~30 ± 7 days after last dose**	**Every 8 weeks**	**Every ~3 months**
Allowed time window				**-2 days[6]**	**± 2 days**	**± 2 days**	**± 2 days[6]**	**± 2 days**	**± 3 days**	**± 3 days**			**±7 days**	
Coagulation		-14 to -1 X[12]												
Urinalysis[11,13]		-14 to -1 X[12]												
Serum pregnancy test[14]		-7 to -1 X												
Urine pregnancy test[15]							X		X	X	X			
CT or MRI[16]		X	EVERY 8 WEEKS ± 7 DAYS								X		X	
Tumor antigens [17]		X	EVERY 8 WEEKS ± 7 DAYS								X		X	
HBV/HCV tests [18]		X	As clinically indicated											
TMZ Dosing Dose escalation			**Pulsed Dosing (Arm A):** Once daily on Days 1 to 7 or Days 1-14 of each 28 day cycle **Continuous Dosing (Arm B)**: Once daily continuously											
TMZ Dosing Dose Expansion			RP2D= 60 mg QD 60 mg QD Days 1-7 of each cycle											
Pamiparib Dosing			60 mg twice daily continuously											
Adverse events		X	X	X	X	X	X	X	X	X	X	X		
Concurrent medications[19]		X	X	X	X	X	X	X	X	X	X	X		
PK assessments[20]			X	X	X									
Blood sample collection for biomarkers[21]		X	X		X						X			
Archival Tumor Tissue or fresh tumor tissue[22]	X		X											
Fresh Tumor Tissues[23] (Dose Escalation and Dose Expansion Cohorts 1-5;	X		X		X						X			

Assessments	Pre-Screening (Dose Expansion only)[1]	Screening[2]	Cycle 1 (28 days)				Cycles 2- 5 (28 days)		Cycle 6 and Subsequent Cycles in 1st year (Every 28 days)	Subsequent Cycles in the 2nd year and beyond (Every 28 days)	EOT[3]	Safety Follow-up[4]	Efficacy Follow-Up	Survival Follow-Up[5]
Day of Phase	**-84 to -29**	**-28 to -1**	**1**	**7**	**15**	**22**	**1**	**15**	**1**	**1**	**~7 days after last dose**	**~30 ± 7 days after last dose**	**Every 8 weeks**	**Every ~3 months**
Allowed time window				**-2 days[6]**	**± 2 days**	**± 2 days**	**± 2 days[6]**	**± 2 days**	**± 3 days**	**± 3 days**			**±7 days**	
additional consent required)														
Survival Status														X

ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end-of-treatment; MRI: magnetic resonance imaging; PK: pharmacokinetic; TMZ: Temozolomide;
X: to be performed.
Notes: All assessments must be performed before investigational product administration in each cycle (except as otherwise noted).

1. **For Dose Expansion Only**: Patients with an unknown germline or somatic *BRCA* mutation or unknown HRD for Expansion Cohorts 1 (ovarian cancer), 2 (TNBC), 3 (mCRPC) and Cohort 6 (multiple indications) will undergo pre-screening for HRD testing for a period of up to 8 weeks prior to eligibility screening (Section 8.1). A separate pre-screening informed consent must be obtained. Any tissues taken during pre-screening period will not be re-collected during the screening period.
   For Dose Escalation Only: Cycle 1 encompasses the 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).
2. Screening must occur within 28 days of Day 1. Assessments obtained within 4 days of Day 1 do not have to be repeated on Day 1. Some assessments have a narrower screening window as shown in the table. Patient registration may occur as late as Day 1 prior to any study treatment.
3. The EOT visit will occur within 7 days after a patient permanently discontinued study drugs for any of the reasons outlined in Section 8.4. 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 CT or MRI showed progressive disease may be used as the EOT visit provided that all required assessments were performed. If routine laboratory tests (e.g., hematology, clinical chemistry) were completed ≤ 7 days before the EOT Visit, these tests do not need to be repeated. The CT/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 progressive disease. ECG does not have to be repeated if it was performed within 14 days of the EOT visit. If the EOT Visit did not occur until 30 days (± 7 days) or later after the last dose of pamiparib and TMZ, the EOT Visit may also be used as the Safety Follow-up Visit.
4. All patients who permanently discontinue study drugs will have a safety follow-up approximately 30 days after the last day of study drugs to collect AEs and SAEs that may have occurred after the patient discontinued from the study drugs. If the patient does not require any laboratory assessments, the investigator or his/her designee will contact the patient to collect this information. (Protocol Section 8.5.1).
5. Following permanent discontinuation of study drugs and/or Safety Follow-up parts of the study, every effort should be made to follow up with all patients by phone every 3 months for their survival status until patient death (Protocol Section 8.5.3).

6. A window of ±2 days on Cycle 1 Day 7 and Cycle 2 Day 1 is allowed during **Dose Expansion Only**.
7. Complete physical examination includes the following items: 1) general appearance; 2) head, eyes, ears, nose, and throat; 3) neck; 4) heart; 5) chest (including lungs); 6) abdomen; 7) extremities; 8) skin; 9) lymph nodes; 10) cardio-vascular; 11) neurological status.
8. A limited physical examination should 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 worsening abnormalities should be recorded as AEs if appropriate.
9. A single 12-lead ECG will be performed during Screening within 14 days of Cycle 1 Day1 and at the EOT visit.
10. **For Dose Escalation and Dose Expansion Cohorts 1-5 Only:** ECGs will be performed in triplicate within a 5-minute window **prior** to Pamiparib PK assessments on Day -2 or Days 1 and 15. ECGs collected on the days of PK assessment will be performed on a machine provided by the sponsor and will be sent to a central reader. The same machine should be used for each patient whenever possible.
11. Hematology includes hemoglobin, platelet count, white blood cell count, neutrophil count, and lymphocyte count.
    Chemistry includes albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, chloride, creatinine, glucose, lactate dehydrogenase, phosphate, potassium, sodium, total bilirubin, and total protein.
    Urinalysis includes blood, glucose, ketones, protein, red blood cells, and white blood cells.
    In the event of clinically significant laboratory results, such as neutropenia (absolute neutrophil count < 1000/mm3), thrombocytopenia (platelets <50,000/mm3), or Grade ≥ 3 clinical chemistry toxicity (per NCI CTCAE v4.03), these assessments will be conducted as frequently as the investigator feels is necessary until toxicity resolves to Grade ≤ 2.
12. Screening blood and urine tests must be performed within 14 days of Day 1. If they were performed within 4 days of Day 1 they do not need to be repeated on Cycle 1 Day 1.
13. If urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated (Section 7.6.3).
14. Only in women of childbearing potential; a serum pregnancy test must be taken ≤ 7 days from Cycle 1, Day 1.
15. For subsequent pregnancy testing on study and at EOT, urine pregnancy tests are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.
16. A computed tomography (CT) or MRI scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed once every 8 weeks ± 7 days to assess all known disease. A CT/MRI taken within 28 days (Screening Period) of Cycle 1 Day 1 does not need to be re-taken. Patients without PD at the EOT Visit should be followed with tumor assessments every 12 weeks (± 7 days).
17. Blood tumor antigens such as CA-125 for ovarian cancer and PSA for castration-resistant prostate cancer will be tested during screening and every 8 weeks ± 7 days after the first dose of pamiparib in local laboratories. The CA-125 responses must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.
18. Testing will be performed by local laboratory at screening and as clinically indicated and will include HBV/HCV serology (hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, and HCV antibody) and viral load assessment (HBV DNA and HCV RNA).
19. Concurrent medications will be collected during screening and on the first day of study. Changes to Concurrent medications will be collected during subsequent clinic visits.
20. Pharmacokinetic (PK) samples will be collected at the following timepoints: For pamiparib: ≤ 30 min before pamiparib and TMZ dosing, 1 (± 15 min), 2 hours (± 30 min), and 4 hours (± 30 min) after pamiparib dose on Cycle 1 Day 1 and Cycle 1 Day 15; For TMZ: on Cycle 1 Day 1 and Day 7 at ≤ 30 min before dosing and 1 hour (± 15 min) after TMZ dose.
21. Blood samples must be collected at screening or on Day 1 for the assessment of germline *BRCA* and/or other mutation analysis (8 ml). In addition, two blood samples (10 mL each) must be collected for plasma markers (e.g., CNA), TMZ treatment, and PARP inhibition **before** study treatment on Day 1 and

Day 15, 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 Study Manual.

22. For patients in Expansion Cohorts 1 (ovarian cancer), 2 (TNBC), and 3 (mCRPC) with unknown *BRCA* mutation or HRD status, collection of archival tumor tissue is required during pre-screening to determine eligibility. For patients in Dose escalation and Cohorts 4 and 5, collection of archival tumor tissue for the purpose of biomarker analysis is required, if available and can be collected on screening or Cycle 1 Day 1. For patients in Cohort 6, collection of an archival tumor tissue sample is mandatory for prospective HRD testing to determine eligibility and should be collected during the prescreening period. Specific instructions for tissue collection and shipment are provided in the Study Manual. **Any tissue provided during pre-screening period will not be re-collected during screening stage**.

23. **For patients in Dose escalation, and patients in Dose expansion Cohorts 4 and 5:** a fresh baseline biopsy of a tumor lesion is highly recommended if archival tissue is not available. Written patient consent is required for fresh tumor biopsies.
For patients with unknown mutation or HRD status in Expansion Cohorts 1 (ovarian cancer), 2 (TNBC), and 3 (mCRPC) or patients in Expansion Cohort 6: if archival tumor tissue is not available, a fresh biopsy must be provided for prospective HRD testing at prescreening. Patients will only be required to sign the prescreening consent form. **Any tissue taken during pre-screening period will not be re-collected during screening stage**.
Dose escalation and Dose expansion Cohorts 1-5: An optional biopsy for pharmacodynamics analysis on Cycle 1 Day 1 and, if agreeable, also on Cycle 1 Day 15 is highly recommended. Optional biopsy will also be taken, if agreeable, at the EOT visit for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanisms. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy (See Section 7.9.2)

Appendix 1 Table 2: Schedule of Assessments and Procedures for PK Intensive Visit (Days -2 to 1): Only for Approximately 20 Patients - Dose Escalation ONLY

Assessments	Day -2 (± 3 days) [1]							Day -1	Day 1
Time	**Pre-dose**	**0 h**	**0.5 h**	**1 h**	**2 hr**	**4 h**	**6 h**	**24 h**	**48 h**
Allowed time window			**± 5 min**	**± 15 min**	**± 30 min**	**± 30 min**	**± 30 min**	**± 2 h**	**± 2 h**
Concurrent medications	X								
Complete Physical examination[2]	X								
Limited physical examination[3]									X
Vital signs (including weight)	X						X	X	X
ECOG performance status	X								
Hematology	X								
Clinical chemistry	X								
Coagulation	X								
Urinalysis[4]	X								
Blood sample collection for biomarkers[5]	X								
Computed tomography or MRI[6]	X								
Triplicate ECGs[7]	X			X	X	X	X		
Pamiparib PK assessments[8]	X		X	X	X	X	X	X	X
Pamiparib Dosing[9]		X							X
Archival Tumor Tissues[10]	X								
Fresh Tumor Tissues[11] (additional consent required)	X								
Adverse events	X							X	X
TMZ Dosing[12]									X
TMZ PK assessments[13]									X

CT: Computerized tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; MRI: magnetic resonance imaging; PK: pharmacokinetic;
TMZ: Temozolomide; X: to be performed.
Notes: All assessments except for post-dose ECGs and PK samples and biopsies must occur before pamiparib administration. ECGs must occur before PK sampling and biopsies must be performed after all ECGs have been completed on Day -2. For patients enrolled into the PK intensive part of the study, the pre-dose biopsy must occur **after** the patient was approved for enrollment and **before** dosing on Cycle 1 Day -2.

1. Screening must occur within 28 days of Day -2. Assessments obtained within 4 days of Day -2 do not have to be repeated on Day -2. Patient registration may occur as late as Day -2 prior to any study treatment.
2. Complete physical examination includes the following items: 1) general appearance; 2) head, eyes, ears, nose, and throat; 3) neck; 4) heart; 5) chest (including lungs); 6) abdomen; 7) extremities; 8) skin; 9) lymph nodes; 10) cardio-vascular; 11) neurological status.
3. A limited physical examination should 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 worsening abnormalities should be recorded as AEs if appropriate.
4. If urine protein is ≥ 2+ by dipstick, a 24-hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated (Section 7.6.3).
5. Blood samples will be collected **before** study treatment on Day -2 for the assessment of germline *BRCA* and/or other mutation analysis (8 ml). In addition, two blood samples (10 mL each) must be collected for plasma markers (e.g., CNA), TMZ treatment, and PARP inhibition. Instructions for the processing, storage, and shipping of samples will be provided in the Study Manual.
6. A computed tomography (CT) or MRI scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed.
7. ECGs will be performed in triplicate on Day -2 within a 5-minute window **prior** to pamiparib PK assessments. ECGs for each patient should be obtained from a calibrated machine provided for the study and the same machine must be used for all ECG assessments on Day -2. Triplicate ECGs will be sent to a central reader.
8. Pamiparib PK samples will be collected at the following timepoints: For pamiparib: ≤ 30 min before dosing on Day -2 and post-dose at 30 min (± 5 min); 1 hour (± 15 min); 2 hours (± 30 min), 4 hours (± 30 min), and 6 hours (± 30 min), 24 hours (± 2 h) on Day -1, and 48 hours (± 2 h) on Day 1.
9. Pamiparib dosing must occur after the collection of the 48-hour post-dose PK sample on Day 1.
10. Collection of archival tumor tissue for purpose of biomarker analysis is highly recommended. Specific instructions for tissue collection and shipment are provided in the Study Manual.
11. In the absence of archival tumor tissues, a fresh baseline biopsy of a tumor lesion is highly recommended. **Any tissues taken during pre-screening period will not be re-collected during baseline**. An optional biopsy for biomarker analysis after treatment on Cycle 1 and if agreeable, also on Cycle 1 Day 15, and EOT is highly recommended. Optional biopsy will also be taken at the EOT visit for the patients who have confirmed disease progression during the study from accessible tumor sites to obtain samples to explore resistance mechanisms. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written patient consent is required for fresh tumor biopsies. Fresh biopsies should be limited to readily accessible tumor lesions (e.g., skin, peripheral lymph nodes, lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis.
12. TMZ dosing must occur after the collection of the 48-hour post-dose PK sample on Day 1.
13. TMZ PK samples will be collected at the following timepoints: pre-dose (within 30 min prior to dose) and 1 hour (± 15 min) post dose.

APPENDIX 2. 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 risk associated with the study treatment). Total sexual abstinence should only be used as a contraceptive method if it is in line with the Patient's usual and preferred lifestyle. Periodic abstinence (e.g., 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 3. NEW YORK HEART ASSOCIATION CLASSIFICATION

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. 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, e.g. walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

NYHA = New York Heart Association

APPENDIX 4. 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 (hypericum perforatum)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calcium channel 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

APPENDIX 5. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES

The text below was obtained from the following reference:
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228-47.

DEFINITIONS

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and

these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression” (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific

guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

RESPONSE CRITERIA

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: The appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case reports recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and progressive disease, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure". While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scans that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be

used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-progressive disease: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression (see comments below) of existing non-target lesions. (Note: The appearance of one or more new lesions is also considered progression).

When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increased diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace"

to “large,” an increase in lymphangitic disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy”. If “unequivocal progression” is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions. However, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it truly represents new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progressive disease based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is progressive disease. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not progressive disease.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study until the end of the study taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy, so protocols should be clear if post-treatment

assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response. The patient's best overall response will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Furthermore, it also depends on the nature of the study, the protocol requirements, and result measurements. Specifically, in non-randomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response". The best overall response is determined once all the data for the patient is known.

Best overall response determination in studies where confirmation of complete or partial response is not required. Best response in these studies is defined as the best response across all timepoints (for example, a patient who has SD in Cycle 1, PR in Cycle 2, and progressive disease in the last cycle has a best overall response of PR). When SD is believed to be best overall response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best overall response, the patient's best overall response depends on the subsequent assessments. For example, a patient who has SD in Cycle 1, progressive disease in Cycle 2 and does not meet minimum duration for SD, will have a best overall response of progressive disease. The same patient lost to follow-up after SD in Cycle 1 would be considered unevaluable.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non- progressive disease	No	PR
CR	Not evaluated	No	PR
PR	Non- progressive disease or not completely evaluated	No	PR
SD	Non- progressive disease or not completely evaluated	No	SD
Not completely evaluated	Non- progressive disease	No	NE
Progressive disease	Any	Yes or No	progressive disease
Any	progressive disease	Yes or No	progressive disease
Any	Any	Yes	progressive disease

CR = complete response; NE = unevaluable; PD = progressive disease; PR = partial response; SD = stable disease

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded, even though the nodes are normal, in order to not overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In studies where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be clearly explained in determination of response. For example, in most studies it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response, it is a reason for stopping study therapy.

Conditions that define "early progression, early death, and unevaluability" are study specific and should be clearly described in each protocol (depending on treatment duration, treatment cycle).

In some circumstances, it may be difficult to distinguish local lesion from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that biopsy be conducted before the local lesion is assigned a status of complete response. FDG-PET may be used to confirm a response to a CR in a manner similar to a biopsy in cases where a local radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the case. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy (including resolution/sensitivity). For equivocal findings of progression (e.g., very small and uncertain new lesions, cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

In non-randomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has been confirmed in such studies. However, in all other circumstances, i.e., in randomized studies (phase II or III) or studies where stable disease or progressive disease are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6 to 8 weeks).

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent or progressive disease is objectively documented.

The duration of stable disease is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the

smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of progressive disease). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint in a particular study, the protocol should specify the minimal time interval required between two measurements for determination of stable disease. Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment cycle, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

APPENDIX 6. DRUGS THAT PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES PROHIBITED MEDICATIONS

Antiarrhythmics	amiodarone disopyramide dofetilide flecainide ibutilide procainamide quinidine sotalol
Anticancer	arsenic trioxide vandetanib
Antihistamines	astemizole terfenadine
Antibiotics	azithromycin clarithromycin erythromycin moxifloxacin sparfloxacin
Antianginal	bepridil
Antimalarial	chloroquine halofantrine
Antipsychotics	chlorpromazine haloperidol mesoridazine pimozide thioridazine
Antinausea	domperidone droperidol dolasetron (intravenous and oral)
Anti-infective	pentamidine
Antilipemic	probucol
Antidepressants	citalopram
Opiate agonists	levomethadyl methadone
GI stimulant	cisapride

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 co-administered 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 (e.g., Torsade de Pointes).

Strong CYP2C8 Inhibitors

gemfibrozil

APPENDIX 8. 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, e.g., light housework, 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.,	

APPENDIX 9. EVALUATION OF RESPONSE ACCORDING TO CA-125

The text below was obtained from the following reference:
Gordon John Sampson Rustin, etc. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST v1.1 and CA-125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21: 419-423.

Definition of Response:

A CA-125 response is defined as at least a 50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained by using the next scheduled CA-125 data (at least 28 days). Patients can be evaluated according to CA-125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

To calculate CA-125 responses accurately, the following rules apply:

- Intervening samples and the 28-day confirmatory sample must be less than or equal to (within an assay variability of 10%) the previous sample.

- Variations within the reference range of CA-125 levels will not interfere with the response definition.

- For each patient, the same assay method must be used, and the assay must be tested in a quality control scheme.

- Patients are not evaluable by CA-125 if they have received mouse antibodies (unless the assay used has been shown not to be influenced by human anti-mouse antibody4, 5) or if there has been medical and/or surgical interference with their peritoneum or pleura during the previous 28 days (e.g., paracentesis). If assessing therapy that includes 2 treatment modalities for relapse (e.g., surgery and chemotherapy), any CA-125 response results from both treatment modalities. CA-125 cannot distinguish between the effects of the 2 treatments.

The date when the CA-125 level is first reduced by 50% is the date of the CA-125 response. To calculate response, an intent-to-treat analysis should be used that includes all patients with an initial CA-125 level of at least twice the upper limit of the reference range as eligible and evaluable. In addition, as a separate analysis, those patients who have a CA-125 response and whose CA-125 level falls to within the reference range can be classified as CA-125 complete responders. In Appendix 9 Table 1 and Appendix 9 Table 2 CA-125 is stated as normalized or normal, means within the reference range. Patients who have a fall of CA-125 to within the reference range but whose initial CA-125 was less than twice the upper limit of the reference range have not had a CA-125 response and cannot therefore be classified as a CA-125 complete responder.

Reporting of response according to GCIG criteria that integrate CA-125 response with RECIST v1.1 is shown in Appendix 9 Table 1 and Appendix 9 Table 2.

Appendix 9 Table 1: Evaluation of best overall response in patients without initial measurable disease and who are evaluable by CA-125

CA-125	Nontarget Lesions*	New Lesions	Overall Serological Response	Best Response for This Category Also Requires
Response and Normalized	CR	No	CR	Confirmed and maintained for at least 28 days
Response	Non-progressive disease	No	PR	
Normalized but no response	Non-CR/Non-progressive disease	No	SD	
Non-PR/non-progressive disease	Non-progressive disease	No	SD	
Progressive disease	Any	Yes or No	progressive disease	
Any	progressive disease †	Yes or No	progressive disease	
Any	Any	Yes	progressive disease	

1. *Nontarget lesions include ascites and peritoneal thickening, which are not measurable according to RECIST.
2. †Unequivocal progression in nontarget lesions may be accepted as disease progression.
3. CR: Complete response; PR: partial response; SD: stable disease.

Appendix 9 Table 2: Best overall response in patients with measurable disease and who are also evaluable by CA-125

Target Lesion*	Nontarget Lesions†	New Lesions	CA-125	Overall Best Response	Best Response for This Category Also Requires
CR	CR	No	Normal	CR	Best RECIST v1.1 response for CR and PR also required it to be confirmed and maintained for at least 28 days if response is primary end point
CR	Non-CR Non-progressive disease	No	Not progressive disease	PR	
CR	CR	No	PR but not normal	PR	
CR	NE	No	PR	PR	
PR	Non-progressive disease or NAE	No	Not progressive disease	PR	
NAE	Non-progressive disease	No	PR	PR	
Progressive disease or New >28 days from CA-125 PR‡			PR	PR	
SD§	Non-progressive disease	No	PR	PR	
SD§	Non-progressive disease or NAE	No	Not PR and not progressive disease	SD	
Progressive disease or New >28 days from CA-125 PR‡			PR	progressive disease	
Progressive disease	Any	Yes or No	Any	progressive disease	
Any	progressive disease	Yes or No	Any	progressive disease	
Any	Any	Yes	Any	progressive disease	
Any	Any	Yes or No	progressive disease	progressive disease	

1. *Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST v1.1.
2. †Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST v1.1.
3. ‡Patients who have a CA-125 response that occurs more than 28 days from PD according to RECIST v1.1 are considered a PR, according to best response, but PD if the RECIST v1.1 PD is within 28 days of CA-125 response.
4. §The protocol should specify the minimum time interval between 2 measurements for classification as stable disease. NE, Not evaluated; NAE, not all evaluated.

APPENDIX 10. PROSTATE CANCER CLINICAL STUDIES WORKING GROUP 2 (PCWG2) CRITERIA TO GUIDE ASCRIBING DISEASE RESPONSE

The table below is modified from the following reference:
Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical studies for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol, 2008. 26(7): 1148-59.

Variable	PCWG2 (2007)
PSA	On this study serial PSA measurements will be done every 8 weeks ± 7 days after the first dose of Pamiparib in the first year and every 9 weeks ± 7 days afterwards. Increases and decreases will be tracked in order to assess disease response. The PSA readings on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG 2: • PSA partial response is defined as a ≥ 50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value. This PSA decline much be confirmed to be sustained by a second PSA value obtained 4 or more weeks later. • PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 4 or more weeks later. The first PSA reading will be obtained at week 12. **Duration of PSA Response:** Duration of PSA response is calculated from the time the PSA value first declines by at least 50% of the Cycle 1 Day 1 (baseline) value that has been confirmed by a second value until the time there is an increase of 25% of PSA nadir, provided the absolute increase is at least 2 ng/mL. The increase must be confirmed by a second consecutive measurement that is at least 25% above the nadir. If the PSA never shows a 25% increase over the nadir value, then the patient will be assessed at the last PSA measurement.

Target Lesions	Nodal or visceral progression sufficient for study entry independent of PSA measurable lesions not required for entry. Use RECIST to record soft-tissue (nodal and visceral) lesions as target or non-target. Only lymph nodes ≥ 2 cm in diameter should be used to assess for a change in size. Record presence of nodal and/or visceral disease separately. Progression at any scheduled reassessment ≥ 12 weeks does not need to be confirmed.
Bone	≥ 2 new lesions at the first scheduled reassessment ≤ 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post-treatment scan (i.e. a total of ≥ 4 new lesions compared with the baseline bone scan). Confirm ambiguous results by other imaging modalities (e.g., CT or MRI). Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
	≥ 2 new lesions at the first scheduled reassessment > 13 weeks from Cycle 1 Day 1 compared with baseline must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared to the baseline scan. (i.e. a total of ≥ 2 new lesions compared with the baseline bone scan). Confirm ambiguous results by other imaging modalities (e.g., CT or MRI). Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.

CT: computed tomography; MRI: magnetic resonance imaging; PCWG2: Prostate Cancer Clinical Trials Working Group 2;
PET: positron emission tomography; PSA: prostate-specific antigen; PSA-DT: PSA doubling-time;
RECIST: Response Evaluation Criteria in Solid Tumors

APPENDIX 11. SIGNATURE OF INVESTIGATOR

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

Protocol Number: BGB-290-103

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. 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, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

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

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

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Approval	[redacted] Clinical Development 19-Jun-2020 21:48:47 GMT+0000

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