NCT03914742

Version Date – 07/07/2022
Previous Version: 01/30/19, 7/26/19, 12/16/19, 4/9/20, 7/29/20

Phase I/II Study of Pamiparib (BGB-290) with Temozolomide in Recurrent Gliomas with IDH1/2 Mutations

A Protocol of the Adult Brain Tumor Consortium (ABTC)

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Investigational Agents: Pamiparib (BGB-290)
IND # 141204 NSC# 803412
Commercial Agent: Temozolomide
IND Sponsor: David Schiff, MD, ABTC Consortium
Other Sponsors: BeiGene & CTEP/DCTD/NCI

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1.0 OBJECTIVES

1.1 Primary Objectives

Phase I Portion:

- Determine the safety and tolerability of the combination of pamiparib (BGB-290) and temozolomide (TMZ) in patients with recurrent IDH1/2 mutant glioma, including the maximum tolerated dose (MTD) and characterization of dose-limiting toxicities (DLTs) in the Phase I portion.

Phase II Portion:

- Determine the overall response rate of pamiparib (BGB-290) with TMZ in patients with recurrent IDH1/2-mutant gliomas that have progressed on TMZ and another alkylator (Arm A) in the Phase II portion.
- Determine the overall response rate of pamiparib (BGB-290) with TMZ in patients with recurrent IDH1/2-mutant glioma that have failed one alkylator with ≥ 12 months since last treatment (Arm B) in the Phase II portion.

1.2 Secondary Objectives

- Determine the progression-free survival (PFS) and overall survival (OS) after treatment with pamiparib (BGB-290) and TMZ in recurrent IDH1/2-mutant gliomas in Arms A and B.
- Determine the duration of response to therapy in recurrent IDH1/2-mutant glioma.
- Confirm the safety and tolerability of pamiparib (BGB-290) in combination with TMZ.

1.3 Exploratory Objectives

1. Assess tumor response rates, PFS, and OS in patients with WHO grade IV glioblastoma (GBM) treated with pamiparib (BGB-290) and TMZ.
2. Assess the mutational landscape via whole-exome sequencing (WES).
3. Assess gene expression patterns using RNA sequencing (RNAseq).
4. Assess the methylation profiling with Infinium Methylation Assays.
5. Quantify 2-hydroxyglutarate (2HG) in archival FFPE specimens via LC-MS detection and correlate with treatment response.
6. Correlate response with 2HG levels, somatic alterations, gene expression/methylation patterns in FFPE tumor tissue.
7. Assess tumor tissue pamiparib (BGB-290) levels, 2HG, and PARylation in a patient subset treated with drug prior to re-resection.

8. Evaluate changes in tumor growth rate in subjects with non-enhancing glioma based on fluid attenuated inverse recovery (FLAIR) tumor volume measurements of serial MRI exams.
9. Assess if change in tumor growth rate (based on FLAIR tumor volume) in subjects with non-enhancing glioma before and after treatment is associated with progression by Response Assessment in Neuro-oncology for Low Grade Gliomas (RANO LGG; phase II patients only) or survival.

2.0 BACKGROUND AND RATIONALE

2.1 Study Disease

The estimated incidence of primary neuroepithelial tumors in the United States is 6.62 per 100,000 person-years, with 15% of those WHO grade II-III gliomas and 60% WHO grade IV glioblastoma (GBM)[1]. Though treatment and natural history vary widely depending on histology and molecular markers, most patients are recommended to undergo maximal safe resection and subsequent radiotherapy and/or chemotherapy. The presence or absence of IDH1/2 mutation is essential to the updated 2016 WHO classification of central nervous system tumors[2], informing prognosis and optimal treatment selection. Among patients with WHO grade II and III glioma, the majority exhibit IDH1/2 mutation[3]. Patients with lower-grade glioma (LGG) and IDH1/2 mutation are most responsive to treatment and have the best prognosis, especially when combined with codeletion of 1p/19q. Patients with GB exhibit IDH1/2 mutation in about 10% of cases and also have a more favorable course than patients who are IDH1/2 wildtype. Regardless of molecular markers, most patients eventually succumb to their disease with local recurrence and progression once effective systemic therapy and radiation therapy options run out. The present trial will enroll patients diagnosed with recurrent glioma WHO grades II-III with IDH1/2 mutation. As an exploratory analysis, patients with GB will also be enrolled and analyzed separately.

2.2 Rationale for selected approach and trial design

2-Hydroxyglutarate (2HG) exists as two enantiomers, (R)-2HG and (S)-2HG, and both are implicated in tumor progression via their inhibitory effects on α-ketoglutarate (αKG)-dependent dioxygenases. The former is an oncometabolite that is induced by the neomorphic activity conferred by isocitrate dehydrogenase-1 and -2 (IDH1/2) mutations, while the latter is produced under pathologic process such as hypoxia. A recent novel discovery was made that IDH1/2 mutations induce a homologous recombination (HR) defect that renders tumor cells exquisitely sensitive to Poly (ADP-Ribose) polymerase (PARP) inhibitors. Remarkably, this "BRCAness" phenotype can be completely reversed by treatment with small molecule inhibitors of mutant IDH1, and, conversely, it can be entirely recapitulated by treatment with exogenous 2HG addition. We localized the mechanism of action to two αKG-dependent dioxygenase targeted by 2HG, KDM4A and KDM4B, which mediate HR suppression. IDH1-dependent PARP inhibitor sensitivity can be demonstrated in a range of clinically relevant models, including primary patient-derived glioma cells in culture and genetically-matched tumor xenografts *in vivo*. A proposed model is presented in Fig. 1. In parallel, two laboratories independently reported a similar synthetic lethal interaction between IDH1/2 mutations and PARP inhibitors, which further strengthens the validity of this interaction [4]. Collectively, these findings directly challenge the current therapeutic strategy to block IDH-mutant function, and they instead provide a novel approach to treat these tumors with PARP inhibitors. Furthermore, these results uncover an unexpected link between oncometabolites, altered DNA repair, and genetic instability.

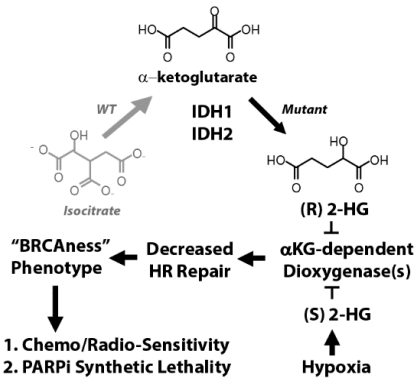


Fig. 1. Proposed mechanism of action of mutant IDH1/2-induced BRCAness and consequent PARP inhibitor synthetic lethality.

In this concept proposal, these findings are directly translated into a biomarker-driven Phase I/II clinical trial. The efficacy of pamiparib (BGB-290), a potent PARP inhibitor known to have adequate central nervous system (CNS) penetration, will be tested in two separate arms (both with TMZ) in patients with recurrent IDH1/2-mutant glioma. While PARP inhibitors have been tested previously in clinical trials with newly diagnosed and recurrent glioblastoma (GB) patients, these trials did not adequately enrich for gliomas harboring IDH1/2-mutations. IDH1/2 mutations are less commonly seen in GB (only 5-10%), and nearly all of these studies inadvertently excluded tumors most likely to harbor mutations in these genes (e.g., tumors that had transformed from a lower grade). The present study will be among the first of its kind specifically to target IDH1/2-mutant gliomas using a cytotoxic, rather than a cytostatic approach.

The prevailing strategy to treat IDH1/2-mutant cancers has been to suppress 2HG production with small molecule inhibitors of the mutant proteins. The rationale for this approach is as follows: oncometabolites appear to drive tumorigenesis, and thus removing them will stop tumor growth. However, there is conflicting pre-clinical data supporting this approach in glioma, which is highlighted by two publications: (1) Rohle

et al. demonstrated modest mutant IDH1 inhibitor activity in a single patient-derived glioma *in vivo*, and similar results were observed using shRNAs which target *both* WT and mutant IDH1 proteins in cells [5]; versus (2) Johannessen *et al.* suggested that while mutant IDH1/2-induced 2HG is critical for initial transformation in glioma, it is dispensable after tumor formation [6]. Three other independent groups have also shown that mutant IDH1/2 inhibitors have *modest* or *no* growth inhibitory effects, using both patient-derived models and primary glioma cell lines [7-9].

In clinical trials, these inhibitors do not appear to have activity in contrast-enhancing gliomas, and at best they maintain stable disease in non-enhancing gliomas, although the latter tumor type is known for indolent growth[10]. In cholangiocarcinoma, a recent phase I trial reported a 5% partial response (PR) rate; 56% patients had stable disease (SD), and the remaining progressed. The 12-month progression-free survival rate was 20.7% [11]. For comparison, a review of 2nd line chemotherapy in cholangiocarcinoma reported median response rates (RRs) of ~8% [12]. These findings suggest that inhibiting mutant IDH1/2 activity may not be effective in solid tumors. In contrast, these inhibitors appear to show activity in IDH1/2-mutant AML. For example, the mutant IDH2 inhibitor, enasidenib, is now FDA-approved for relapsed IDH2-mutant AML. The approval was based on a non-randomized phase I/II trial [13] which demonstrated an overall RR of 40%, with a median response duration of 5.8 months. Of note, the mutant IDH2 clone persisted in the bone marrow of all patients treated. Thus, while these inhibitors have shown promise in AML, they are unlikely to be curative for most cancers with IDH1/2 mutations.

Clinical data supporting the hypothesis that oncometabolite production should be exploited rather than suppressed, is therefore needed in an expedited fashion. The planned correlative studies will investigate appropriate pharmacokinetic and pharmacodynamic endpoints associated with this therapeutic approach. Should this hypothesis be correct, a new and effective standard of care could be identified for patients with recurrent glioma and IDH1/2 mutations, which would potentially impact both PFS and OS in a positive manner.

IDH1/2-Mutant Tumors Harbor an HR Defect and are Sensitive to PARP inhibitors

Overview of our recent discovery. IDH1/2 mutations induce an HR defect that renders tumor cells sensitive to PARP inhibition. The mechanism of action for this interaction is summarized in Fig 1 above. This novel and unexpected phenotype was validated across five unique and genetically diverse cell line pairs that were engineered to express either the wild-type (WT) or the mutant IDH1/2 proteins, and the observed DSB repair defect was confirmed using multiple orthogonal functional assays. This interaction has been demonstrated in a number of clinically relevant models, including IDH1/2-mutant primary patient-derived cell lines and genetically-matched tumor xenografts. This work was recently published in *Science Translational Medicine* [14]. Representative data from this study are presented below to support the rationale for the proposed clinical study. In addition, new and unpublished preliminary data are presented here which support the rationale for testing PARP inhibitors in IDH1/2-mutant gliomas.

IDH1/2-mutants harbor an intrinsic HR defect leading to exquisite PARP inhibitor sensitivity. 2HG induces BRCAness using a collection of engineered, isogenic IDH1/2-WT and -mutant cell lines. These cell lines were created using three orthogonal approaches: (a) recombinant adeno-associated virus (rAAV) targeting, (b) CRISPR/Cas-based gene targeting, and (c) stable transfection with doxycycline (dox)-inducible IDH1/2-WT and -mutant open reading frames (ORFs). Mutant IDH1/2 protein expression and 2HG production in these systems was validated by LC-MS/MS, and then profiled them for DNA repair defects and DNA repair inhibitor sensitivity. Cells with DSB repair defects have elevated rates of baseline DSBs that engage DDR proteins, which can be detected using neutral comet assays and via DDR foci visualization [9,15-17]. Marked elevations in unrepaired DSBs in all of the IDH1/2-mutant cells were detected tested using comet assays, which correlated with increased γH2AX and 53BP1 foci at baseline. Of note, 53BP1 foci formation are indicative of true DNA DSBs [18]. In parallel, exquisite PARP inhibitor sensitivity was identified in IDH1/2-mutant cells, which was observed with multiple unique drugs in this class (nearly 50-fold with olaparib). Representative data are shown for the HCT116 IDH1-WT and -mutant cell line pair in Fig. 2. Of note, HCT116 are and ideal system to assess metabolic changes associated with TCA disruption [19], and they were used previously in seminal work on mutant IDH1 function [20,21].

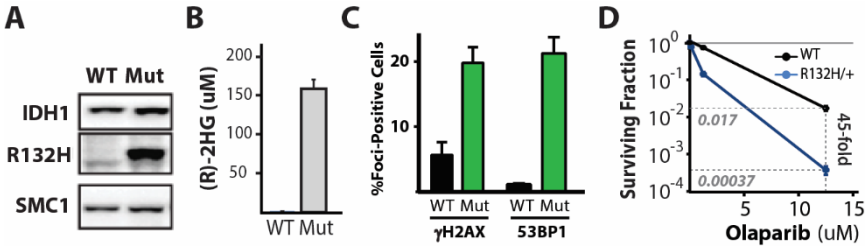


Fig. 2. Representative data in HCT116 IDH1-WT/mutant cells demonstrating: **(A)** mutant protein expression, **(B)** upregulated R-2HG; which correlates with **(C)** increased baseline DDR foci, and **(D)** exquisite PARP inhibitor sensitivity.

R- and S-2HG block directly block HR repair. The mutant IDH1/2 phenotype presented above is strikingly similar to that seen in BRCA-deficient cells, which prompted the interrogation of the integrity of HR. Using a plasmid HR reporter assay, the expression of mutant, but not WT, IDH1/2 was found to have significantly suppressed HR. Based on these data, the effects of R-2HG directly on HR were tested using the chromosomally- integrated HR reporter assay, DR-GFP, in IDH1-WT U2OS cells. These cells were chosen because they are widely used as a tool to measure factors that impact HR [22]. R-2HG significantly suppressed HR in a dose-dependent manner, and similar phenotypes were observed with the (S) enantiomer. HR

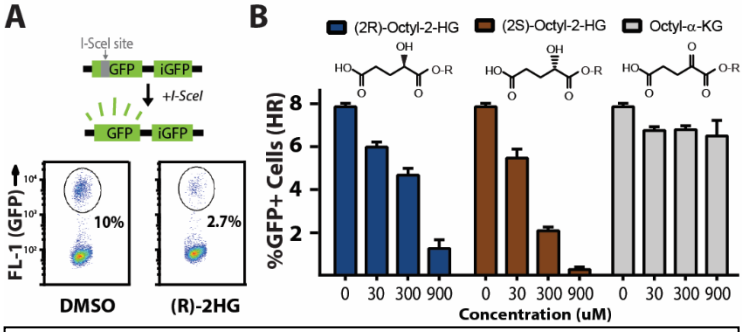


Fig. 3. 2HG suppresses HR. DR-GFP reporter assay schematic and representative flow cytometry data shown in (A). Dose-dependency for both R- and S-2HG, but not αKG, shown in (B).

suppression approached levels seen with siRNAs targeting two key HR genes, RAD51 and BRCA2. In contrast, treatment with a cell permeable αKG did not affect HR repair under these same *conditions*. Representative are shown in Fig. 3 from recently published work [18].

2HG-mediated HR suppression is mediated via KDM4A/B inhibition. There are over 60 dioxygenases which utilize α-KG as a co-factor [23,24], which includes JmjC domain-containing KDMs and the TET family of 5-methylcytosine (5mC) hydroxylases [25-27]. A focused siRNA screen of all genes in this family to identify mediators of the mutant IDH1/2-induced HR defect, using a miniaturized DSB repair profiling platform developed by the Bindra laboratory [28]. This screen identified KDM4A and KDM4B, which was confirmed using multiple unique siRNAs targeting each gene. Representative data are shown in Fig. 5, using comet assays to monitor the mutant IDH1/2-induced DNA repair defect. In these experiments, siRNAs targeting either KDM4A or KDM4B in IDH1-WT cells led to an increase in unrepaired DSBs, which was similar to that observed in IDH1-mutant cells (Fig. 4a). However, these siRNAs did not increase DSBs further in the IDH1-mutant cells, which suggests an epistatic interaction. Conversely, overexpression of KDM4A or KDM4B, but not other key dioxygenase proteins, specifically rescued the mutant IDH1-induced DNA repair defect (Fig. 4b).

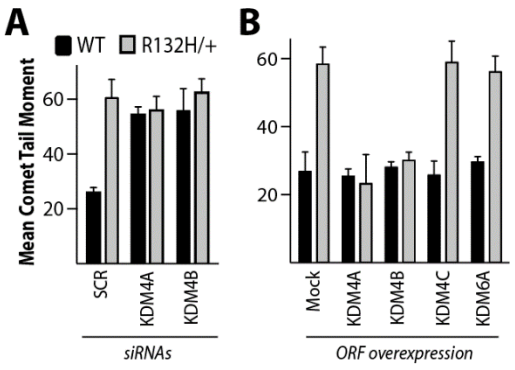


Fig. 4. The mutant IDH1/2-induced DNA repair defect is (A) phenocopied by siRNA knockdown of KDM4A/B, and (B) rescued by overexpression of the corresponding ORFs.

IDH1/2 mutants confer exquisite *in vivo* PARP inhibitor sensitivity. Using a flank xenograft model in mice, the activity of PARP inhibitors against IDH1-mutant tumors were tested *in vivo*. A mutant IDH1-dependent synthetic lethal interaction in isogenic HCT116 and HeLa cell line pairs with olaparib was confirmed, and olaparib activity in tumor xenografts derived from HT0180, a fibrosarcoma cell line which harbors an endogenous IDH1 R132C mutation, was demonstrated. Significant *in vivo* activity was demonstrated with another PARP inhibitor, BMN-673. Representative data are shown for the HCT116 cell line pair with olaparib in Fig. 5.

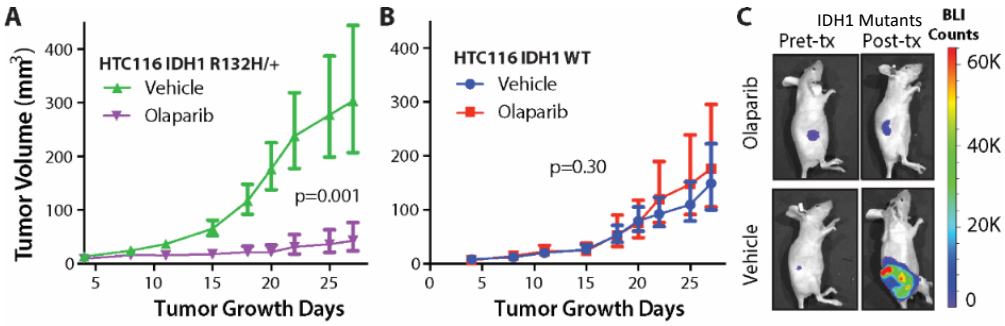


Fig. 5. (A) PARP inhibitors selectively kill HCT116 IDH1-mutant tumor xenografts with **(B)** minimal effects on IDH1-WT cells; **(C)** BLI monitoring of treatment responses.

Demonstration of PARP inhibitor sensitivity in IDH1/2-mutant glioma models. Attempts were made to detect a mutant IDH1/2-induced PARP inhibitor sensitivity phenotype in model tumor cell lines which were more relevant to glioma. To this end, PARP inhibitor sensitivity in well-characterized, previously published immortalized astrocyte cell line containing a doxycycline (dox)-inducible R132H-mutant IDH1 ORF were tested [29]. As

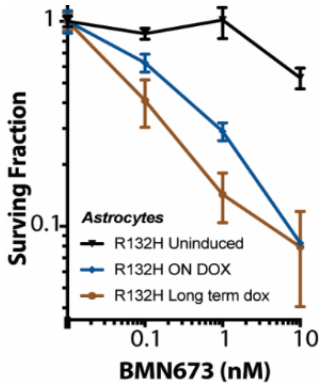


Fig. 6. PARP inhibitor sensitivity in an immortalized astrocyte cell line with a stable, dox-inducible mutant

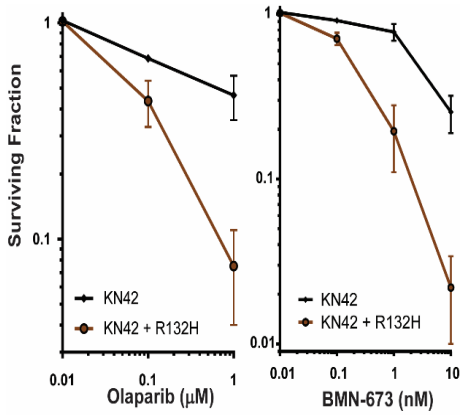


Fig. 7. PARP inhibitor sensitivity a model glioma cell line, KNS42, with a dox-inducible mutant IDH1 ORF.

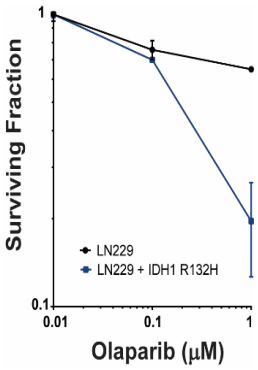


Fig. 8. PARP inhibitor sensitivity a model glioma cell line, LN229, with a dox-inducible mutant IDH1 ORF.

shown in Fig. 6, both transient and long-term induction of mutant IDH1 protein expression conferred marked levels of BMN-673 sensitivity, as detected by clonogenic survival analysis. Next, similar dox inducible mutant IDH1 systems were created in two additional human glioma cell lines, KNS42 and LN299, and were treated with several unique PARP inhibitors. As shown in Fig. 7, mutant IDH1 expression in KNS42 induced robust sensitivity to both olaparib and BMN-673. Similar results were obtained in our engineered LN229 cell line (Fig. 8).

In addition, multiple aspects of the IDH1/2-induced BRCAness phenotype were demonstrated in a range of clinically relevant, primary models *in vitro*, including patient-derived glioma cell lines. For example, a collection of early-passage, patient-derived IDH1-WT and -mutant glioma cell lines available at our institution were tested (clinical characteristics are shown Fig. 9a, which includes tumors with oligodendroglioma features). IDH1 mutations were confirmed by sequencing previously [30], and 2HG production was confirmed in the corresponding samples (Fig. 9b). Baseline persistence of DSBs were demonstrated by comet assay in the IDH1-mutant cell lines (Fig. 9c), which is a classic approach to assess functional DSB repair activity. Although these are early-passage, primary cells obtained directly from fresh glioma resection tissue, clonogenic survival assays in a subset were performed. We detected PARP inhibitor sensitivity in the IDH1-mutant primary glioma cultures #96 compared to two IDH1-WT cultures (#2 and #129) by clonogenic survival, and once again we found that 2HG exposure recapitulated PARP inhibitor sensitivity in WT cultures (Fig. 9d). These data confirm the ability to detect an IDH1-associated DSB repair defect in grades 2-4 glioma.

A

Table 1: Primary Culture Collection - Patient Information

Patient ID	IDH Status	Grade	Tumor Histology	Age	Sex	MGMT
2	R132C	3	Anapl. Astro	30	M	n/a
35	R132H	2	Oligoastro	51	F	n/a
61	R132H	2	Oligoastro	26	M	n/a
64	R132H	2	Astrocytoma	49	M	n/a
80	WT	4	Glioblastoma	45	F	UM
97	WT	2	Oligodendro	57	M	n/a
129	R132H	3	Oligoastro	46	M	n/a
138	R132H	4	Glioblastoma	33	F	M
141	WT	2	Oligoastro	57	M	M
180	WT	4	Glioblastoma	17	F	UM

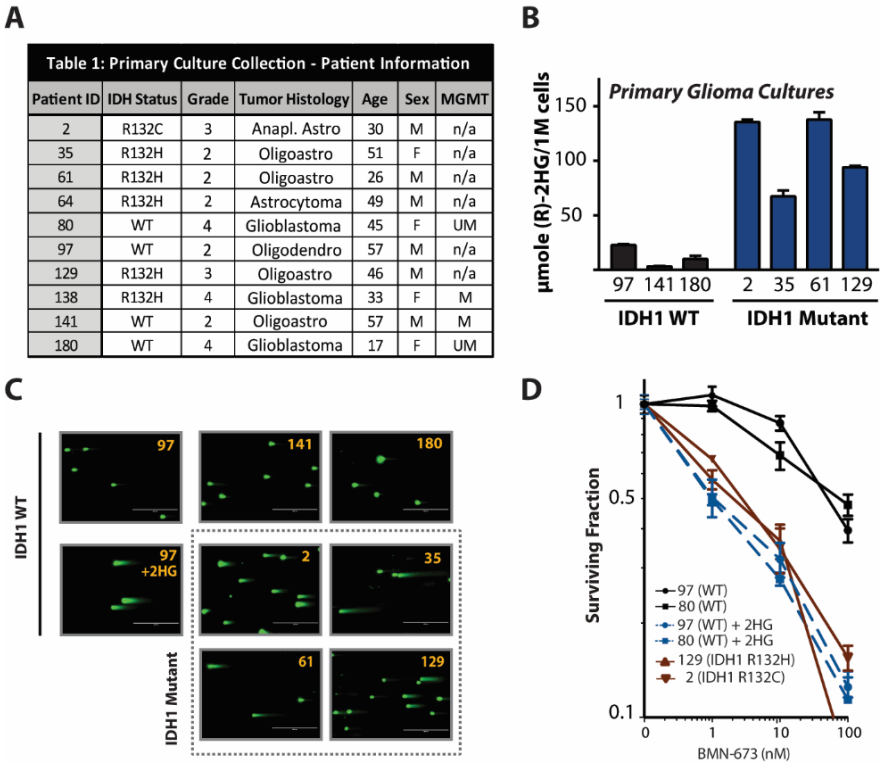


Fig. 9. Demonstration of the HR-defective and PARP inhibitor sensitivity phenotype in primary, patient-derived glioma cultures.

<u>Mutant IDH1/2 synthetic lethality correlates with PARP trapping activity of PARP inhibitors.</u> Recent studies indicate that PARP inhibitors that specifically "trap" PARP protein at sites of DNA damage are most effective against IDH1/2-mutant cells. Examples of PARP-trapping PARP inhibitors include: BMN-673, niraparib, rucaparib pamiparib (BGB-290), and olaparib [31]. In contrast, veliparib, while very effective as a catalytic inhibitor of PARP function, is an extremely poor PARP-trapper [31]. These PARP inhibitors were profiled for synthetic lethality with IDH1-mutant vs. –WT cells, which confirmed activity with these PARP-trapping PARP inhibitors, and also that veliparib was not effective under these conditions. Representative data for pamiparib (BGB-290) are presented below in Figs. 10 and 11, and data for olaparib and BMN-673 were presented above.

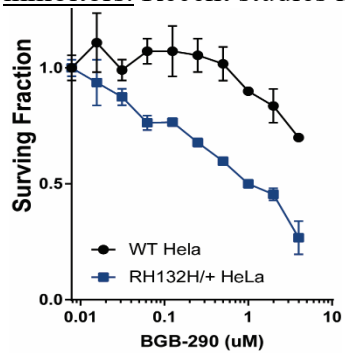


Fig. 10. Confirmation of PARP-trapping PARP inhibitor sensitivity with BGB-290 in IDH1-mutant versus –WT cells.

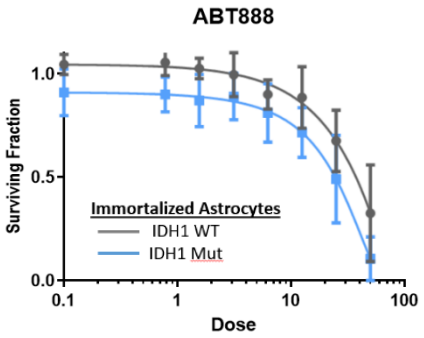


Fig. 11. Veliparib is not synthetic lethal with IDH1-mutant cells.

Enhanced synergistic interactions between PARP inhibitors and DNA damaging agents in IDH1/2-mutant cells. Synergistic interactions have been reported when PARP inhibitors are combined with DNA damaging agents in both HR-deficient and -proficient tumors [32,33], which prompted testing for synergy here. Synergy interactions were assessed using the Combenefit program, an open-access software tool that enables the visualization, analysis and quantification of drug combination effects [34]. IDH1-WT and -mutant cells were profiled in short-term growth inhibition assays with a collection of DNA damaging agents to assess baseline differential sensitivity. These studies revealed modest, but detectable sensitization with cisplatin, methyl methanesulfonate (MMS), and irinotecan as single agents (data not shown). However, substantial synergistic interaction was observed between cisplatin and BMN-673 in IDH1-mutant tumor cells (Fig. 12). Similarly, substantial synergy between TMZ and PARP inhibitors in IDH1-mutant cells was observed (representative data is shown in Fig. 13 for reference).

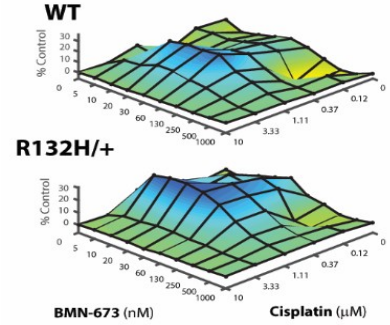


Fig. 12. PARP inhibitor synergism with cisplatin, which is most pronounced in IDH1-mutant cells (blue=synergistic interaction).

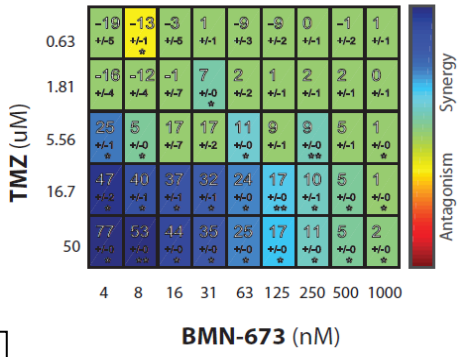


Fig. 13. PARP inhibitor synergism with TMZ in IDH1-mutant cells (blue=synergistic interaction).

IDH1/2 Mutations Persist in Recurrent Glioma

Recent data from the Gunel laboratory at Yale indeed showed that IDH1 mutations in gliomas that are initially present at diagnosis appear to persist after recurrence [30], though there are rare exceptions[35]. Similarly, persistence of the IDH1 mutation has also been found in relapsed AMLs that harbored the mutation at initial diagnosis [36]. Thus, it would be expected that there will be persistent 2HG production and HR deficiency in recurrent IDH1/2-mutant tumors, making this group a suitable population for the current study.

Clinical Efficacy of Synthetic Lethal Targeting of HR Defects with PARP inhibitors

Olaparib is an orally bioavailable PARP inhibitor that has been approved by the FDA as the first monotherapy to treat BRCA-mutant advanced ovarian cancer [37]. PARP is involved in surveillance and maintenance of genome integrity and functions as a key molecule in the repair of DNA single-stranded breaks (SSBs) [38]. PARP-inhibited cells accumulate unrepaired SSBs leading to double strand breaks when encountered by the replication machinery. Based on the principle of synthetic lethality, treatment with single-agent PARP inhibitor has a dramatic therapeutic impact in a proportion of patients with germ-line or tumor-based (somatic) mutations in BRCA1 or BRCA2. Favorable response

data have also been observed in a subset of patients without evidence of BRCA1/2 mutations, and there is emerging consensus that other molecular alterations in DNA repair pathways, including HR deficiency, can increase the likelihood of response to PARP inhibitors [39,40]. There are now three FDA-approved PARP inhibitors for the treatment of HR-deficient ovarian cancer, and it is likely that several more will be approved in the next 2-3 years. Robust response rates have been observed with these agents, often with PFS improvements in the range of 2-5 fold compared to control groups [41].

The use of PARP inhibitors in IDH1/2-mutant tumors is analogous to the rationale used for treating BRCA-deficient cells with a PARP inhibitor. As 2HG accumulates in IDH1-mutant cells, HR is disrupted which causes cells to rely on alternative low fidelity DNA repair pathways, thus hastening genomic instability and cell death. This creates a "BRCAness" phenotype that renders them increasingly susceptible to agents that impair the DNA damage response and to those that cause additional DNA damage, including ionizing radiation and platinum-containing drugs.

PARP Inhibitor Testing in Glioma Clinical Trials

Several PARP inhibitors have been tested in glioma clinical trials thus far. Prior to the discovery that IDH1/2 mutations induce BRCAness and PARP inhibitor sensitivity, the rationale for these trials was in part based on findings that GBs are known to harbor a high prevalence of genetic alterations that affect DNA repair pathways. Alterations in PTEN are reported in 34% of GBs, leading to upregulation of epidermal growth factor (EGFR)/phosphatidylinositol-3-OH kinase (PI3K) signaling pathway resulting in defects in homologous recombination [42]. In mouse embryonic PTEN -/- cells, defects in the regulation of RAD51 expression are notable [43]. Synthetic lethality with PTEN loss and PARP inhibition with veliparib have shown preferential sensitivity in human GB cell lines compared to those cells with intact PTEN [44]. For this reason, PARP inhibition has been hypothesized to offer a particularly strong benefit in GB patients and thus several clinical trials have enrolled these patients (NCT02152982 as above, NCT01390571, NCT00687765, and NCT02974621).

In this context above, PARP inhibitors are typically combined with DNA damaging chemotherapies such as TMZ. TMZ induces methylation predominantly at the O-6 and N-7 positions of guanine which are repaired by different mechanisms. The generation of O-6-methylguanine is repaired in cells expressing the suicide enzyme, O-6-methylguanine methyl transferase (MGMT). Silencing of the MGMT gene by promoter methylation occurs in slightly over one-half of all GB patients [45] conferring a significant prognostic benefit and increased sensitivity to TMZ. Low grade oligodendrogliomas, oligoastrocytomas, and astrocytomas frequently have high frequencies of MGMT promoter methylation and are sensitive to TMZ. Of note, it is now well accepted that IDH1/2-mutations correlate with MGMT promoter methylation, with the former likely driving the latter via the induction of a methylator phenotype [29].

With regard to the mechanism of action of TMZ sensitivity, O-6-methylguanine mispairs with thymine during replication. Mismatch repair machinery identifies this mispairing, attempts futile cycles of thymine reinsertion and excision, and ultimately results in replication fork collapse, double strand breaks, and cell death via apoptosis [46]. With regard to the N-7-methylguanine base damage, this lesion is repaired by a combination of base excision repair (BER) and single strand break repair. PARP inhibitors interfere with the completion step of BER leading to increased DNA damage and apoptosis with TMZ [47,48]. Taken together, PARP inhibitors are thought to sensitize tumor cells to TMZ by inhibiting repair of the induced N-7-methylguanine base damage. This sensitization likely is magnified in the setting of MGMT promoter methylation, in which O-6-methylguanine base damage also accumulates. As noted above, TMZ has also been shown to synergize with PARP inhibitors in HR defective cells via a separate mechanism of action, which likely can be attributed to an increase in collapsed replication forks and consequent one-ended DSBs that require HR for resolution. As such, it is believed that the combination of TMZ and PARP inhibitors, specifically in IDH1/2-mutant gliomas has great potential for marked synergistic interactions; by simultaneously exploiting the HR defect and the effect on alkylation damage repair.

It is important to note that the current trial is the first study that will test the efficacy of PARP inhibition specifically in IDH1/2-mutant gliomas. It is now well established that while 70+% of lower grade gliomas harbor IDH1/2 mutations, these mutations are much less commonly observed in GBs [49]. Specifically, over 90% of GBs arise *de novo* (termed "primary GB"), and IDH1 mutations are rarely found in these tumors. The remaining 10% of GBs predominantly arise from lower grade gliomas (termed "secondary GB"), and thus these tumors, although a minority of all newly diagnosed GBs, frequently harbor IDH1/2 mutations. *These relative differences are critical, as they indicate that clinical trials that use a histologic diagnosis of GB as the sole eligibility criteria will not capture a significant proportion of IDH1/2-mutant tumors in their cohorts.* The relative frequencies of IDH1/2 mutations in all grades and sub-types of gliomas are presented in Fig. 14, which is taken from a comprehensive review on this subject [49]. Another factor is likely to have even further reduced the proportion of IDH1/2-mutant tumors that have been tested in clinical trials with PARP inhibitors: most studies specifically excluded secondary GB and/or tumors with features suggestive of components arising from lower grade gliomas. For example, a Phase II/III randomized Alliance trial (A071102; NCT02152982) is

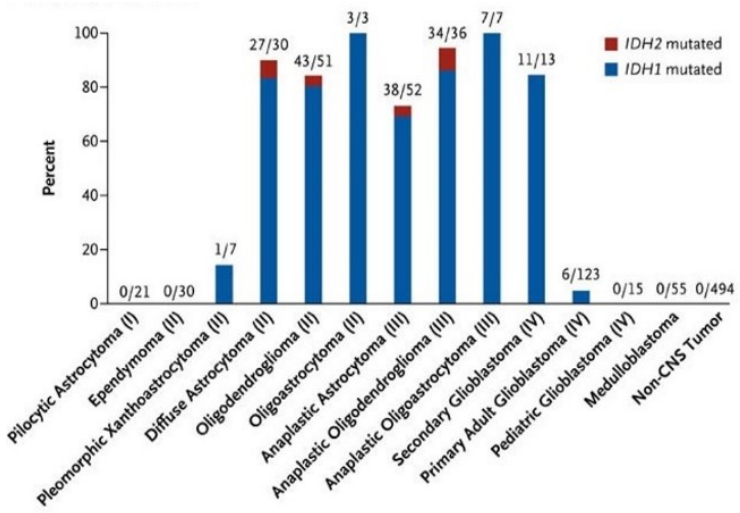


Fig. 14. Overview and distribution of IDH1/2 mutations in glioma.

testing the efficacy of the PARP inhibitor, veliparib, in combination with adjuvant temozolomide in newly diagnosed GB, but it specifically excludes GBs with oligodendroglial features with a 1p19q co-deletion; these tumors commonly harbor IDH1 mutations [50]. As another example, the aforementioned Oparatic Trial in recurrent GB specifically excludes secondary GB [51]. Collectively, these findings suggest that the target glioma population in whom PARP inhibitors have been tested thus far may not have been the optimal experimental cohort. Instead, an ideal group would be composed of patients with IDH1/2-mutant gliomas, and the proposed trial will test this specific group of patients.

Since the initial concept for this trial was developed, additional information regarding the combination of pamiparib (BGB-290) and TMZ has become available. BGB-290-104, a phase I study for patients with first recurrence of glioblastoma, utilized our proposed dose level 1 of pamiparib (BGB-290) 60 mg twice daily and TMZ 40 mg Days 1-21 every 28 days and found this combination exceeded MTD because of neutropenia and thrombocytopenia. Similarly, BGB-290-103, a solid tumor study using the same pamiparib (BGB-290) schedule with TMZ 40 mg daily, noted excessive hematologic toxicity. Both of these studies have de-escalated TMZ to 20 mg daily.

Pre-clinical data supporting the activity of the PARP inhibitor Pamiparib (BGB-290)

As presented above, we have already confirmed that pamiparib (BGB-290) is active against IDH1/2-mutant versus WT cells. However, pamiparib (BGB-290) also has undergone extensive *in vitro* and *in vivo* testing to confirm its activity as (a) a PARP inhibitor that is synthetic lethal with BRCA-deficient tumor cells, (b) a TMZ sensitizer in MGMT WT (um-methylated promoter) tumor cells, and (c) a TMZ sensitizer in MGMT promoter-methylated glioma models. As will be discussed below, these data have formed the basis for pamiparib (BGB-290) testing in several clinical trials, including a trial in newly diagnosed and recurrent GB (not stratified by IDH1/2 mutation status; noting once again that these mutations are rare in GB). In this section, representative pre-clinical data is presented that highlight the activity of pamiparib (BGB-290) both as a monotherapy synthetic lethal agent, and as a TMZ sensitizer.

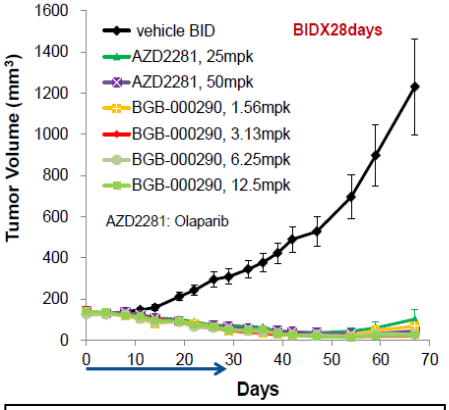


Fig. 15 (AZD2281) in a BRCA1 mutant xenograft mouse model.

As shown in Fig. 15, monotherapy treatment with pamiparib (BGB-290) at a dose of 1.6 mg/kg BID showed similar activity as olaparib dosed at 25 mg/kg BID with regard to tumor growth delay in a BRCA1-mutant mouse xenograft model (MDA-MB-436). This constituted a roughly 16-fold increase in potency for pamiparib (BGB-290) over olaparib. No body weight loss was observed for pamiparib (BGB-290) at all doses tested, and the MTD was 25 mg/kg BID. In a pharmacokinetic (PK)/pharmacodynamic (PD) study, oral

administration of pamiparib (BGB-290) resulted in time- and dose-dependent inhibition of PARylation in the MDA-MB-436 xenografts in mice. Importantly, inhibition of PARylation in the tumor tissues correlated well with tumor drug concentrations of pamiparib (BGB-290). These data indicate that pamiparib (BGB-290) is equally efficacious to, but significantly more potent than olaparib, which is FDA-approved for the treatment of BRCA-mutant metastatic ovarian cancer.

pamiparib (BGB-290) was also shown to synergize with TMZ *in vivo* in an H209 small cell lung cancer xenograft model (Fig. 16). In this model, pamiparib (BGB-290) (2.73 mg/kg BID x 21 days) given as a 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, and the mean tumor volume reached 505 mm^3 on Day 66. The addition of pamiparib (BGB-290) (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 (BGB-290) and TMZ significantly enhanced TMZ anti-tumor activity and delayed resistance. This is particularly important for the present study, since subsets of patients will have had prior exposure to alkylators such as TMZ.

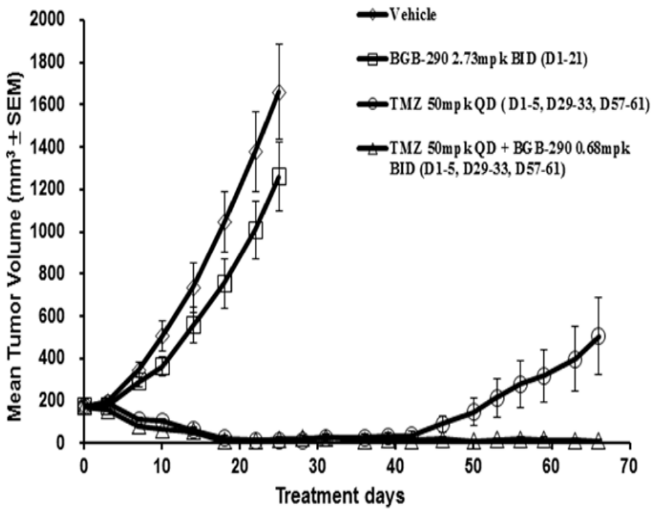


Fig. 16. Combination Activity of BGB-290+TMZ in a H209 Small Cell Lung Cancer Xenograft Model. Diamonds=vehicle; squares=BGB-290 2.73 mg/kg BID on Days 1 to 21; circles=TMZ 50 mg/kg once per day on Days 1 to 5, Days 29 to 33 and Days 57 to 61; triangles=TMZ 50 mg/kg once per day and BGB-290 0.68 mg/kg twice per day on Days 1 to 5, Days 29 to 33 and Days 57 to 61.

	Brain/Plasma (%)
BGB-290 10 mg/kg	18%
Niraparib 50 mg/kg	9%
Olaparib 50 mg/kg	2%
Talazoparib 3 mg/kg	2%
Veliparib 50 mg/kg	38%

Table 1. CNS penetration of selected PARP inhibitors.

As shown in Table 1, pamiparib (BGB-290) was confirmed to have high levels of CNS penetration in mouse models relative to other PARP inhibitors. Though veliparib was found to have superior CNS penetration, its inferiority in terms of PARP trapping makes pamiparib (BGB-290) an appropriate candidate for this particular study. As such, it was also tested whether pamiparib (BGB-290) was active against H209 xenografts grown as

intracranial xenografts. In this particular series of experiments, a TMZ-resistant clone of H209 was tested. This clone was generated by treating H209-xenografted tumors with multiple cycles of TMZ *in vivo* (essentially as presented in Fig. 16). In this model, pamiparib (BGB-290) (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 (Fig. 17). 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 (BGB-290) and TMZ significantly prolonged animal survival compared to TMZ ($p<0.01$), with median survival of 54 days. The result suggests pamiparib (BGB-290) in combination with TMZ can overcome TMZ resistance in this intracranial model.

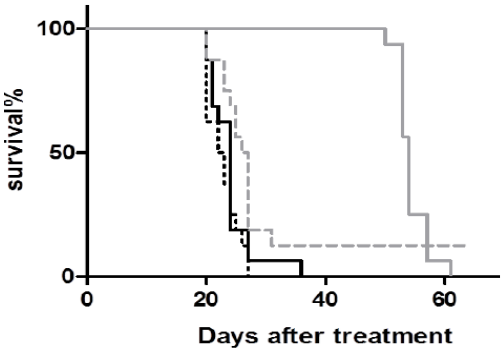
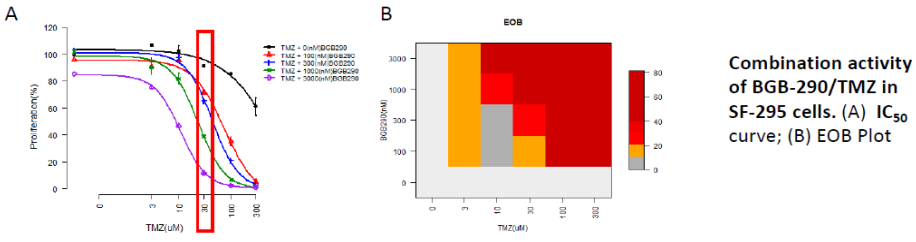


Fig. 17. Combination Activity of BGB-290 and TMZ in an H209-T Intracranial Model. Dashed black line = vehicle; solid black line = BGB-290 2.73 mg/kg twice daily; dashed gray line = TMZ 50 mg/kg once per day for five days; solid gray line = TMZ 50 mg/kg once per day and BGB-290 0.68 mg/kg twice per day on Days 1 to 5, Days 15 to 19 and Days 29 to 33.

Next, the anti-proliferative effect of pamiparib (BGB-290) in combination with TMZ was evaluated in 8 human GBM cell lines resistant to single-agent TMZ (EC50 of 32 µM or greater). In 7 of 8 cell lines, pamiparib (BGB-290) demonstrated synergism with TMZ with a shift in EC50 for TMZ of 5-fold or greater (Fig. 18). This was further extended to an *in vivo* GBM PDX intracranial model, in which it was shown that the combination of pamiparib (BGB-290) and TMZ maximally extended overall survival (Fig. 19). Taken together, these data indicate that pamiparib (BGB-290) is a potent PARP inhibitor and robust TMZ sensitizer, with clear activity in CNS tumor models.

Cell Line	EC50 of TMZ Single Agent (µM)	Number of Cells with EOB	Average EOB per Cell	Max EC50 Shift for TMZ
SNB-19	>300	95%	34.7	>33 fold ↓
SF-295	>300	80%	36.9	>29 fold ↓
T98G	>300	55%	26.9	>8 fold ↓
SF-539	80	80%	19.9	8 fold ↓
U-118MG	>300	70%	24.0	>7 fold ↓
U251	32	80%	20.7	6 fold ↓
LN-229	>300	45%	10.6	>5 fold ↓
U87-MG	>300	50%	10.7	N/A



Combination activity of BGB-290/TMZ in SF-295 cells. (A) IC_{50} curve; (B) EOB Plot

Fig. 18. Assessment of synergistic interactions between pamiparib (BGB-290) and TMZ in GB cell lines. EOB=excess over bliss.

Experience with Pamiparib (BGB-290) in Clinical Trials

PARP inhibition with pamiparib (BGB-290) is currently being studied in two Phase Ia studies (BGB-290-AU-002 in Australia and BGB-290-102 in China), as well as one Phase Ib study (BGB-A317/BGB-290_Study_001) in combination with an anti-PD-1 antibody. The maximum tolerated dose (MTD) was found in the Australian study to be 80 mg PO BID with persistent Grade 2 nausea despite optimal medical therapy being the dose limiting toxicity. Complete or partial responses were observed in subjects with ovarian and related cancers in this study group (representative data is shown in Fig. 20).

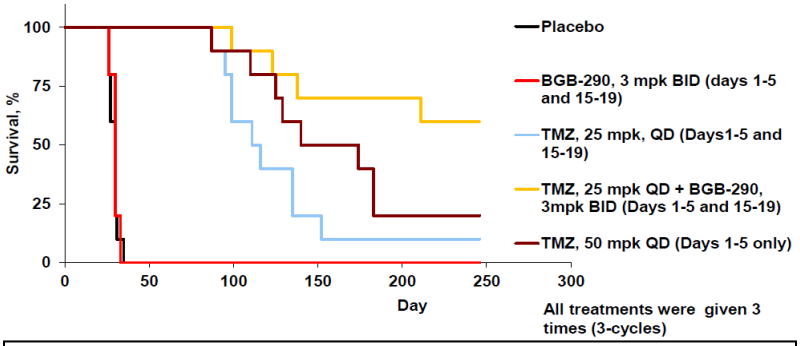


Fig. 19. Activity of Pamiparib (BGB-290)/TMZ in an Intracranial GBM

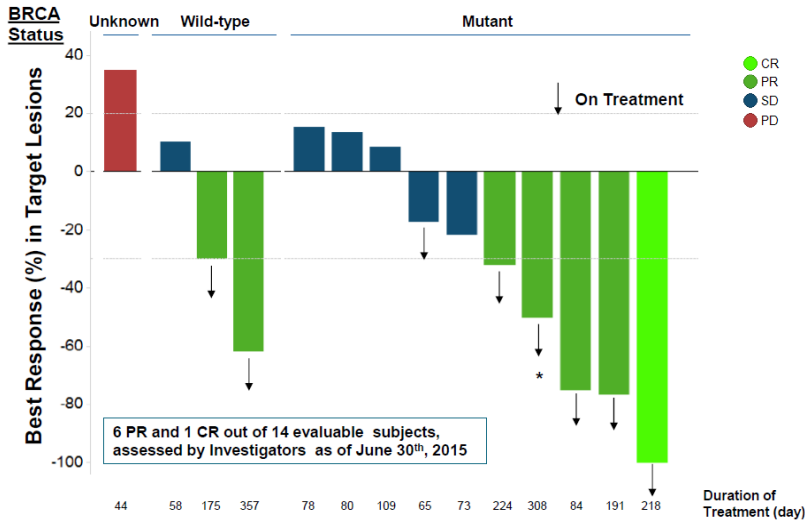


Fig. 20. Pamiparib (BGB-290) response data from the ovarian cancer

A Beigene industry-sponsored trial (IST) with pamiparib (BGB-290) is currently enrolling for newly diagnosed and recurrent GBM. The primary goal of this study is to test whether pamiparib (BGB-290) is active as a radiosensitizer, with or without TMZ, against IDH1/2-WT, MGMT promoter un-methylated GBM. In addition, pamiparib (BGB-290) with TMZ in recurrent GBM is being tested in a separate cohort. As mentioned earlier, these cohorts will not have significant numbers (if any) of IDH1/2-mutant gliomas; and there is no pre-stratification for patients with these tumors.

Background and Rational for low dose Temozolomide

While temozolomide was initially developed as a sensitizer for chemotherapy [52], subsequent laboratory-based studies suggested that the synergistic interaction between PARP inhibitor and chemotherapy often occurred at much lower doses of the latter agent than used previously, most notably for TMZ[53-56]. This has led to a "paradigm shift", which TMZ is used as a sensitizer for PARP inhibitors. As such, a number of trials have

emerged which are testing markedly lower TMZ doses in combination with PARP inhibitors, including pamiparib (BGB-290), dosed at or near their MTD (e.g., NCT03150862, NCT03672773, NCT02049593, and NCT02392793). Of note, Beigene recently presented there preliminary results testing 60 mg BID of pamiparib (BGB-290) with low doses of TMZ (e.g., 20 mg flat dosing) in extracranial metastatic solid tumors, with substantial numbers of responses independent of BRCA1/2-mutation status (ESMO 2018, Poster# 421P). As such, we propose to combine a maximum dose of pamiparib (BGB-290) with low dose TMZ, based on these findings.

Safety Profile of daily low dose Temozolomide

There are extensive safety data on the safety profile of daily low dose temozolomide. Although temzolomide was initially studied using 150-200 mg/m2 on a 5/28 schedule, a published phase II study showed safety and efficacy of 75 mg/m2 on a daily basis during radiation therapy [57]. This same daily schedule was proven to have efficacy and has become the standard of care [58]. Protracted daily dosing of temozolomide at 50 mg/m2 has been utilized with excellent safety and tolerability in the RESCUE study[59]. In ABTC 1801, the dose of temozolomide administered is < 25% that of the RESCUE study; thus, no new safety signals are anticipated.

2.3 Correlatives Studies Background

Overview. A number of exploratory biomarker/correlative studies are proposed in this protocol, which are all essentially focused on identifying key molecular correlates of treatment response.

- **Mutational landscape studies.** We now understand that there are distinct molecular sub-groups in glioma which are associated with distinct patterns of co-occurring mutations, mRNA expression, and DNA methylation [19]. In addition to IDH1/2 mutations, a number of genes are found to be mutated in glioma, including ATRX, CIC, FUBP1 and CDK4. CIC is of particular relevance to this study, because mutations in this gene may correlate with the magnitude of 2HG production that is seen in IDH1/2-mutant tumor cells [20]. Importantly, a recent study reveals that there are three distinct molecular sub-groups, even within IDH1/2-mutant gliomas, each with unique co-occurring gene mutations [21]. These findings have been corroborated by other groups, with implications for treatment response and overall survival [22]. We thus seek to assess the mutational landscape in tumor specimens from patients treated with pamiparib (BGB-290) and TMZ in this study, and to assess whether these mutations correlate with treatment response. We will utilize whole-exome sequencing (WES) to achieve this goal.

- **Assessment of gene expression patterns and methylation profiles.** As noted above, each of the three molecular sub-groups within IDH1/2-mutant gliomas have unique mutational spectra [18]. Low and high glioma CpG Island Methylator Phenotype (G-CIMP) clusters are found within these sub-groups, which correlate with distinct gene expression changes, and which segregate independent of grade and histology [23]. MGMT promoter methylation is found in the majority of IDH1/2-mutant gliomas, although clear

correlations with G-CIMP with regard to MGMT mRNA expression have yet to be defined clearly [24]. MGMT status is important for both TMZ response [25] and also PARP inhibitor sensitization [26], and thus is likely to be an important factor to consider in the response to pamiparib (BGB-290) and TMZ in our study. Collectively, these data suggest that both methylation profiles and gene expression patterns may be important for understanding treatment response this study. As such, we will perform both methylation and gene expression profiling in for all patients using Infinium Methylation Assays and RNA sequencing (RNAseq), respectively.

- **Oncometabolite profiling via LC/MS-MS.** 2HG levels can be significantly affected by (a) allelic and subcellular compartment differences based on specific IDH1/2 mutations [27] and (b) by co-occurring mutations as noted above [28]. As we found a dose-dependent relationship between 2HG and homologous recombination (HR) suppression, these two features many affect the response to pamiparib (BGB-290). The Li laboratory, working in collaboration with the Bindra laboratory, recently established at set of LC-MS/MS protocols to detect oncometabolites in both FFPE and frozen tissue. The Li laboratory has extensive expertise in the use of LC-MS/MS to measure small molecules in tissue for pre-clinical studies and clinical trials [29-31]. Here, we will correlate 2HG levels with pamiparib (BGB-290) and TMZ treatment response using these protocols.

- **Intratumoral drug level assessments via LC/MS-MS.** It is now well-established that the blood-brain barrier (BBB) is a significant obstacle to treatment efficacy for many drugs [32]. Pre-clinical studies indicate that pamiparib (BGB-290) is CNS penetrant, with a brain-to-plasma ratio of ~18%, and intracranial xenograft studies have demonstrated activity of the drug against glioma tumors. However, the extent to which pamiparib (BGB-290) penetrates both enhancing and non-enhancing disease in glioma, in human subjects, is not yet known. As such, we will perform a phase 0 study within this trial, in which patients will be administered pamiparib (BGB-290) for 7 days prior to re-resection. Biopsies will be taken from both enhancing and non-enhancing areas of disease, which will be tested for the presence of pamiparib (BGB-290) by LC-MS/MS. A guide for acceptable approaches to identify and biopsy enhancing and non-enhancing is provided in the study lab manual.

  The molecular landscape of cancer is just beginning to be defined. However, there is inadequate knowledge about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, the goal is to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

  Measurements of Tumor Growth Rate on FLAIR: Radiographic response rate is not the sole imaging endpoint of interest. It is recognized that low-grade gliomas commonly shrink with cytotoxic chemotherapy, but this shrinkage is slow and usually does not meet the 50% threshold to qualify as a partial response by RANO criteria. Additionally,

response rates specifically for molecularly defined (IDHmt) lower-grade gliomas treated with chemotherapy are difficult to glean from the literature. For these reasons, several recent studies (e.g. AG120-881-C-001, AG120-C-002, DFCI/HCC 14-045) have utilized assessment of the rate of growth of FLAIR tumor volume on study treatment compared to the growth rate over the preceding six months to seek a biological signal of activity of the study treatment. Our hypothesis is that even if we do not see an adequate number of RANO-defined responses to meet our primary objective, we may see a marked decline in tumor growth rate in some subjects indicative of meaningful biological activity. The use of volumetric growth rate to determine whether an investigational therapy has an antitumor effect has precedent. For example, ivosidenib was reported to decrease the average tumor growth rate from 24% in the six months preceding treatment to 11% for the six months following treatment initiation in a cohort of 24 patients with progressing non-enhancing IDHmt gliomas (https://doi.org/10.1093/neuonc/nox168.037). Defining a meaningful decrease in growth rate for an individual patient is admittedly somewhat arbitrary; a 100% decrease in growth rate would be an excessive threshold tantamount to completely stable disease. We are proposing a > 50% decrease as potentially biologically meaningful.

3.0 PATIENT SELECTION

3.1 Patient Population

Sample Size:

Phase I, Dose Finding: 6-18 patients.

Phase II: 39-78

Surgical Portion: 10 patients

Accrual Rate:

2–3 patients per month.

Gender:

Male and female.

Age:

Patients must be at least 18 years of age.

Race:

Minorities will be actively recruited. No exclusion to this study will be based on race or ethnicity.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	4	5	1	1	**11**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	7	10	2	4	**23**
White	21	31	5	7	**64**
More Than One Race	2	3	1	2	**8**
Total	**34**	**49**	**9**	**14**	**106**

3.2 Eligibility Criteria

1. Phase I patients must have one of the following: (a) histologically confirmed WHO grade II-III glioma that is progressive or recurrent following at least one prior chemotherapy plus or minus radiation therapy regimen **or** (b) Grade IV disease in their recurrent resection or biopsy specimen **or** (c) Grade IV glioma at initial diagnosis, with recurrent disease.
   Phase I patients may have failed an unlimited number of prior systemic regimens.

   Phase II patients must have histologically confirmed WHO grade II-IV glioma that is progressive or recurrent following therapy:

   Phase 1, Phase II & Surgical Portion: Recurrence in non-enhancing tumors will be defined as 25% or more increase in bi-dimensional product of FLAIR signal abnormality (measurable disease) per the low-grade glioma (LGG) RANO criteria. Contrast-enhancing tumors with measurable enhancing targets will be defined as recurrent based on standard RANO criteria. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

   Patients with recurrent glioma <12 weeks after completion of radiotherapy must have new enhancement outside of the RT field (beyond the high-dose region or 80% isodose line), or evidence of viable tumor on histopathologic sampling.

   - **Arm A** patients must have WHO grade II-III glioma and have failed TMZ and another alkylator (e.g., carmustine, lomustine, procarbazine). Patients in Arm A may have failed an unlimited number of prior systemic regimens. Prior radiotherapy (RT) is not required for eligibility.

   - **Arm B** patients must have WHO grade II-III glioma and have experienced tumor progression after TMZ or another alkylator (maximum one prior chemotherapy regimen), and have gone ≥ 12 months since last treatment (chemotherapy or RT). Prior RT is allowed but not mandated.

- **GBM Arm** patients must have WHO grade IV glioblastoma following radiotherapy (45-60 Gy in 1.8-2.0 Gy fractions) plus chemotherapy and may have failed an unlimited number of prior systemic regimens.

2. **Surgical Portion** patients must have histologically confirmed WHO grade II-IV glioma that is progressive or recurrent following therapy and must be undergoing repeat surgery that is clinically indicated as determined by their care providers. Surgical Portion patients may have had an unlimited number of prior therapy regimens.

3. Phase I and Phase II patients must have available at least 3 prior full sets of MRI scans (not including screening), each separated by at least 2 months. Sites must agree to provide MRI Imaging form within four weeks after treatment start. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

4. Patients must have IDH1/2-mutant glioma. IDH1/2-mutation status can be confirmed by immunohistochemistry (IHC) or direct DNA sequencing, provided that it is performed in a CLIA/CAP-certified laboratory. IDH1/2 mutations must be associated with neomorphic activity of the encoded proteins (i.e. IDH1 R132, IDH2 R172, IDH2 R140, IDH1 R100, IDH1 G97, IDH1 Y139[29]).

5. Patients must have archival FFPE specimens and mutations will be verified centrally, although this will not preclude patients with appropriate documentation of IDH1/2-mutant status from trial enrollment. Patients must have a tumor tissue form indicating availability of archived tissue from a previous surgery, completed and signed by a pathologist; sites must agree to provide this form within 14 days after treatment start. See Section 9.5.1.

6. Patients must have measurable (defined by at least 1 cm x 1 cm) contrast-enhancing disease or measurable abnormal T2/FLAIR hyperintensity indicative of tumor by MRI imaging within 21 days of starting treatment. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

7. Patients must have documented molecular 1p/19q and MGMT testing. If either of these studies has not been performed previously, they can be done prior to enrollment.

8. Patients must be able to undergo MRI of the brain with gadolinium. Patients must be maintained on a stable or decreasing dose of corticosteroid regimen (no increase for 5 days) prior to this baseline MRI. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

9. Patients must have recovered (<CTCAE grade 2 or baseline) from severe toxicity of prior therapy. The following intervals from previous treatments are required to be eligible:

    - 12 weeks from the completion of radiation.
    - 6 weeks from a nitrosourea chemotherapy
    - 3 weeks from a non-nitrosourea chemotherapy
    - 4 weeks from any investigational (not FDA-approved) agents
    - 2 weeks from administration of a non-cytotoxic, FDA-approved agent (e.g., erlotinib, hydroxychloroquine, etc.)

10. Patients must be 18 years of age or older.

10. Patients must have a Karnofsky Performance (KPS) Status ≥ 60% (i.e. the patient must be able to care for himself/herself with occasional help from others).

11. Patients must have the following organ and marrow function:

Absolute neutrophil count	≥1,500/ µL
Platelets	≥100,000/ µL
Hemoglobin	≥ 9 g/dL
Total bilirubin	≤ institutional upper limit of normal
AST (SGOT)/ALT (SGPT)	≤ 4 × institutional upper limit of normal
Creatinine	≤ institutional upper limit of normal
OR	
Creatinine clearance	≥60 ml/min/1.73m^2 for patients with creatinine levels above institutional normal
APTT or PTT	≤ 1.5 × institutional upper limit of normal

12. Patients must be able to provide written informed consent.

13. Women of childbearing potential must have a negative serum pregnancy test within 7 days of first dose. Women of childbearing potential and men must agree to use highly effective contraception (refer to Appendix III for more details) prior to study entry, for the duration of study participation, and for at least 6 months after the last dose of study drug.

    Patients should consult their physician regarding what contraceptive method should be used. It should be noted, however, that barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of birth control or pregnancy prevention and if used must be combined with a highly effective contraceptive method.

    Women of childbearing potential (defined in Appendix III) must also agree to monthly pregnancy tests through 6 months after completion of pamiparib (BGB-290) or temozolomide administration. Should a woman become pregnant or suspect she is

pregnant while she or her partner is participating in this study or within 6 months after completing the study treatment, she should inform her treating physician immediately. The study doctor will monitor the pregnancy at least up to completion and at most up to 8 weeks following the delivery date (refer to Monitoring Pregnancy Section for more details). In addition, women who become pregnant while participating in the study must immediately stop taking study treatment. Men treated or enrolled on this protocol must also agree to use condoms in addition to 1 of the highly effective methods of contraception (listed in Appendix III) prior to the study, for the duration of study participation, and through 6 months after completion of pamiparib (BGB-290) or temozolomide administration. If a female partner of a male patient is already pregnant, the male patient must use condoms during sexual intercourse for the duration of the study and for at least 6 months after the last dose of pamiparib (BGB-290)

Women and men should not donate and/or freeze egg/sperm while participating in the study and for at least 6 months after completing study treatment.

If a woman or man is in an exclusive same-sex relationship and is not engaged in attempts to become pregnant or father a child, it is not necessary to use a highly effective contraceptive method.

14. Patients must have no concurrent malignancy except curatively treated basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix, breast, or bladder. Patients with prior malignancies must be disease-free for ≥ 5 years.

15. Patients must be able to swallow tablets and capsules.

3.3 Ineligibility Criteria

1. Patients receiving any other investigational agents are ineligible.

2. Patients previously treated with a small molecule inhibitor of mutant IDH1/2 proteins are ineligible.

3. Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to pamiparib (BGB-290) are ineligible.

4. Patients who have received bevacizumab within the last 6 months are ineligible.

5. Patients with a known hypersensitivity to TMZ are ineligible.

6. Patients who have received a PARP inhibitor previously are excluded.

7. Patients on enzyme-inducing anti-epileptic drugs (EIAED) are not eligible for treatment on this protocol. Patients may be on non-enzyme inducing anti-epileptic drugs or not be taking any anti-epileptic drugs. Patients previously treated with

EIAEDs may be enrolled if they have been off the EIAED for 10 days or more prior to the first dose of pamiparib (BGB-290).

8. Patients who have not recovered to <CTCAE grade 2 toxicities apart from alopecia related to prior therapy are ineligible.

9. Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, clinically significant cardiac disease, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible.

10. Pregnant women are excluded from this study because the effects of pamiparib (BGB-290) on a fetus are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pamiparib (BGB-290), breastfeeding should be discontinued if the mother is treated with pamiparib (BGB-290).

11. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial

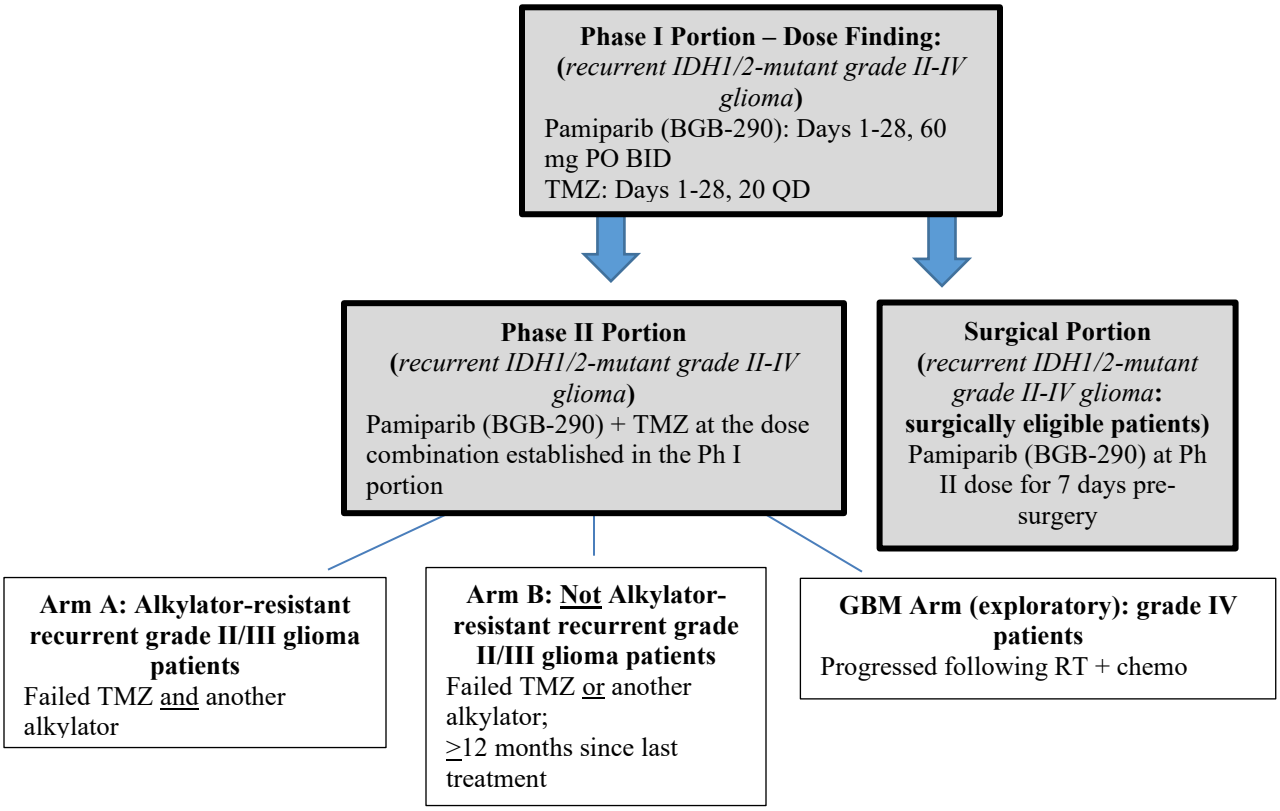
4.0 STUDY DESIGN AND TREATMENT PLAN

This is a multicenter, open-label Phase I/II study of pamiparib (BGB-290) in combination with TMZ in patients with IDH1/2-mutant WHO grade II-IV recurrent glioma. Due to the potential for markedly divergent differences in prognosis between patients with WHO grade II-III versus WHO grade IV tumors, the subset of WHO grade IV tumor patients will be enrolled in a separate exploratory arm in the Phase II portion, utilizing only descriptive statistics to assess response to therapy.

Grade II-III patients in the Phase II portion will be stratified into 2 arms based on the timing of prior alkylator chemotherapy exposure; a third arm will include the subset of glioblastoma (grade IV) patients.

Arm A includes alkylator-refractory, poor risk patients. These patients have recurrent IDH1/2-mutant glioma (WHO grades II/III) who have failed TMZ and another alkylator.

Arm B includes distant alkylator failure, favorable risk patients. These patients have recurrent IDH1/2 mutant glioma (WHO grades II/III) who have failed TMZ or another alkylator (at most one chemotherapy regimen) and have gone ≥ 12 months since last treatment (chemotherapy or RT).



Patients will receive pamiparib (BGB-290) at a dose of 60 mg PO BID on days 1 to 28 of 28-day cycles plus TMZ at a dose to be established in the Phase I portion, until disease progression, unacceptable toxicity, withdrawal of consent, or death.

A subset of patients planning to undergo a biopsy or re-resection will be eligible for a correlative sub-study, in which pamiparib (BGB-290) will be administered for 7 days prior to surgery.

Correlative studies will include pamiparib (BGB-290) drug levels, 2HG production, and PARylation levels in tumor tissue specimens from enhancing and non-enhancing sites of disease in the sub-study.

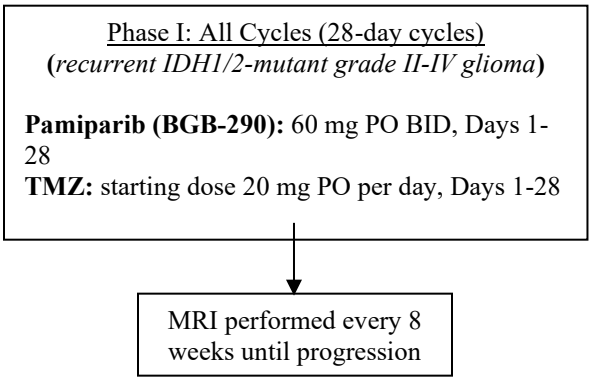
4.1 Phase I Treatment Plan

The Phase I portion will determine the MTD of the combination of pamiparib (BGB-290) and TMZ and will be open to patients with IDH1/2-mutant WHO grade II-IV recurrent glioma.

A single dose level of pamiparib (BGB-290) (60 mg BID) will be tested in combination with flat-dosing of TMZ. TMZ starting dose has been chosen to match active studies by Beigene in newly diagnosed and recurrent GBM (NCT03150862) and solid tumors.

Pamiparib (BGB-290) will be administered orally, in capsule formation, at 60 mg PO BID. Flat-dosing will be used for TMZ. The first dose level of 20 mg QD days 1-28 every 28 days corresponds to 11.5 mg/m^2 assuming an average body surface area of 1.73 m^2. If needed dose levels (-1, -2 and -3) will utilize the same dose for days 1-21, days 1-14, and days 1-7 every 28 days, respectively.

Pamiparib (BGB-290) will be given orally twice daily on Days 1 to 28 of 28-day cycles. TMZ will be given orally once daily on treatment days as defined per the dose level. The safety evaluation period is at the completion of the initial cycle of treatment. The standard 3+3 design will be used for dose-finding. Dose escalation will be done in a stepwise fashion to have 6 patients treated at a putative MTD. The target DLT rate is 33%. The MTD is defined as the dose of pamiparib (BGB-290) in combination with TMZ that yields a dose limiting toxicity rate of less than or equal to 33%.



Patients will be followed by routine blood work, general and neurological examination, and MR imaging. Please refer to the Imaging Core Manual for further imaging requirements and submission information. See Section 9.1 for schedule.

Patients may continue to receive cycles of pamiparib (BGB-290) until tumor progression via LGG RANO (van den Bent et al., *Lancet Oncol* 2011; 12:583-93) or standard RANO, depending on tumor grade at time of treatment, development of unacceptable toxicity, or meeting other criteria for going off treatment (Section 10.1). Patients will be followed for adverse events for at least 30 days after the last dose of pamiparib (BGB-290). All patients will be followed for survival.

4.1.1 Dose Finding

Pamiparib (BGB-290) will be given at 60 mg BID at each dose/schedule; the dose of TMZ will be de-escalated/changing the treatment schedule, as shown in the table below if necessary:

Phase I dose/schedule de-escalation

Dose Level	Pamiparib (BGB-290)	Temozolomide Dose/Schedule
1 (starting dose)	60 mg BID	20 mg QD Days 1-28
-1	60 mg BID	20 mg QD Days 1-21
-2	60 mg BID	20 mg QD Days 1-14
-3	60 mg BID	20 mg QD Days 1-7

*Pamiparib (BGB-290) will be dose reduced only after discussion with Study Chair

The standard 3+3 design will be used for dose finding. Three patients will be enrolled per dose/schedule cohort. If no DLTs are observed in the first 3 patients at Dose Level 1, 3 additional patients will be enrolled at Dose Level 1 before pursuing Phase II of the protocol. If 1/3 of the patients develops a DLT during the first 4 weeks of treatment beginning from the first dose of pamiparib (BGB-290), Dose/Schedule Level 1 (or any subsequent dose/schedule level) will be expanded by 3 additional patients at the same dose/schedule level. The 3 additional patients must be followed for at least 4 weeks and toxicity evaluated before continuing.

Number of Patients with DLT at a Given Dose/Schedule	**Decision Rule**
0 out of 3	Enter 3 more patients at the same dose/schedule
1 out of 3	Enter 3 more patients at the same dose/schedule
2 out of 6	This is the maximum tolerated dose/schedule
2-3 out of 3, or ≥3 out of 6	MTD exceeded, enter 3 patients at next lower dose/schedule

Dose-limiting toxicity (DLT) is defined in Section 5.1. No intra-patient dose escalation is allowed. Patients will be evaluable for the cohort if they have completed at least 80% of their expected dose of pamiparib (BGB-290) for the first treatment cycle (28 days). Patients who experience a DLT will be evaluable for the cohort if they have received at least one dose of pamiparib (BGB-290). The toxicity evaluation period is the first 4 weeks of treatment.

The target DLT rate is 33%. If the MTD is not reached among the pre-specified doses/schedules, the dose for the Phase II portion will be the highest dose/schedule studied for which the DLT rate is ≤ 33% in 6 evaluable patients.

4.2 Phase II Treatment Plan

The Phase II portion will determine the overall response rate of treatment with pamiparib (BGB-290) combined with TMZ at the recommended Phase II dose in patients with recurrent IDH1/2-mutant gliomas. Patients will be stratified into the following arms:

Arm A

Patients who have experienced recent tumor progression despite prior treatment with TMZ and another alkylating chemotherapy (e.g., BCNU, CCNU or procarbazine) have extremely poor treatment response to subsequent chemotherapies[52]. The primary endpoint for the phase II portion will be response rate based on measurable disease. The study assumes the null hypothesis of response rate at 5% and will accept a 25% response rate as a meaningful treatment effect for pamiparib (BGB-290) with TMZ to treat recurrent/progressive IDH1/2-mutant glioma.

Initially, 15 patients will be enrolled into Arm A. This arm of the trial will be stopped if no response is obtained among the first 15 patients (0/15). Otherwise, the study will continue and 10 additional patients will be enrolled into Arm A.

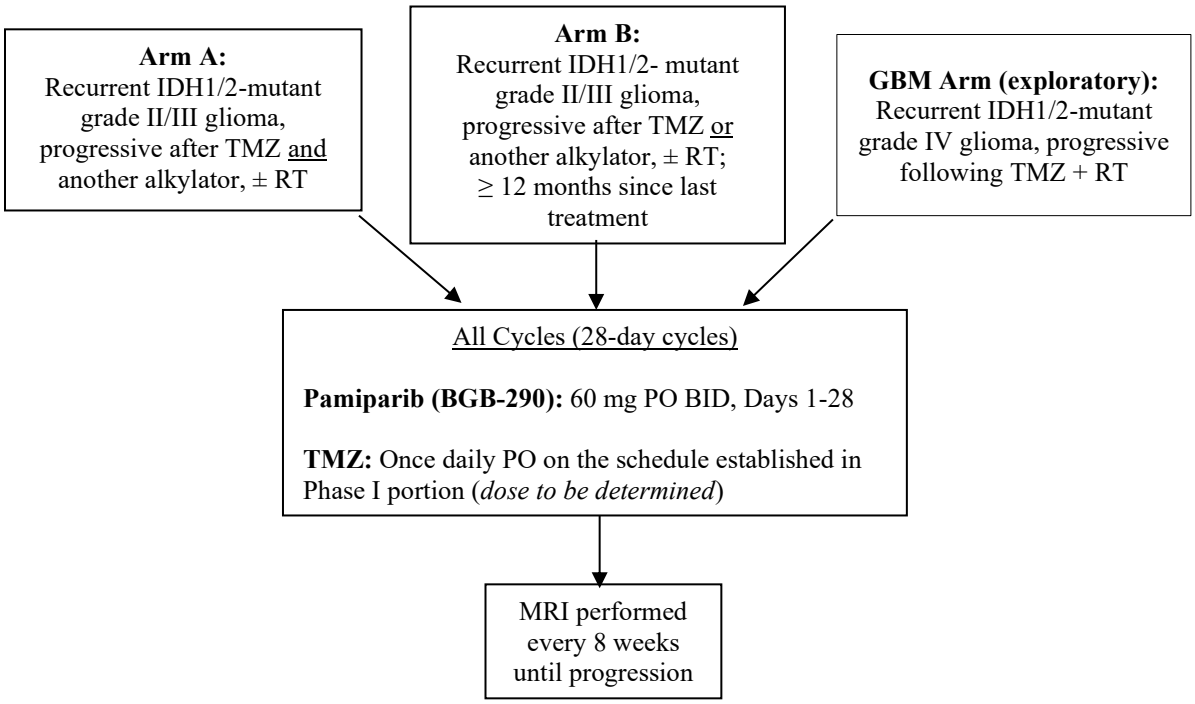
Arm B

Patients who have experienced recent tumor progression after failure of TMZ or another alkylator and have gone ≥ 12 months since last treatment have a more favorable prognosis and show a range from 0-44% response rate when challenged with an alternative alkylating agent-based regimen [60, 61]. The study assumes the null hypothesis of response rate at 30% for the combination regimen and will accept a 50% response rate as a meaningful treatment effect for pamiparib (BGB-290) with TMZ.

Initially, 24 patients will be enrolled into Arm B. This arm of the trial will be stopped if 7 or fewer responses are obtained among the first 24 patients (≤ 7/24). Otherwise, the study will continue and 29 additional patients will be enrolled into Arm B.

GBM Arm (exploratory)

Patients with recurrent WHO grade IV GBM that harbor an IDH1/2 mutation will be enrolled into the exploratory arm and also treated with pamiparib (BGB-290) combined with TMZ. Due to the small fraction of patients with these tumors among all recurrent grade IV GBM (~5%), the study will enroll no more than 10 patients into this arm. This group will be analyzed separately from the primary cohorts and their response rates will be reported using descriptive statistics



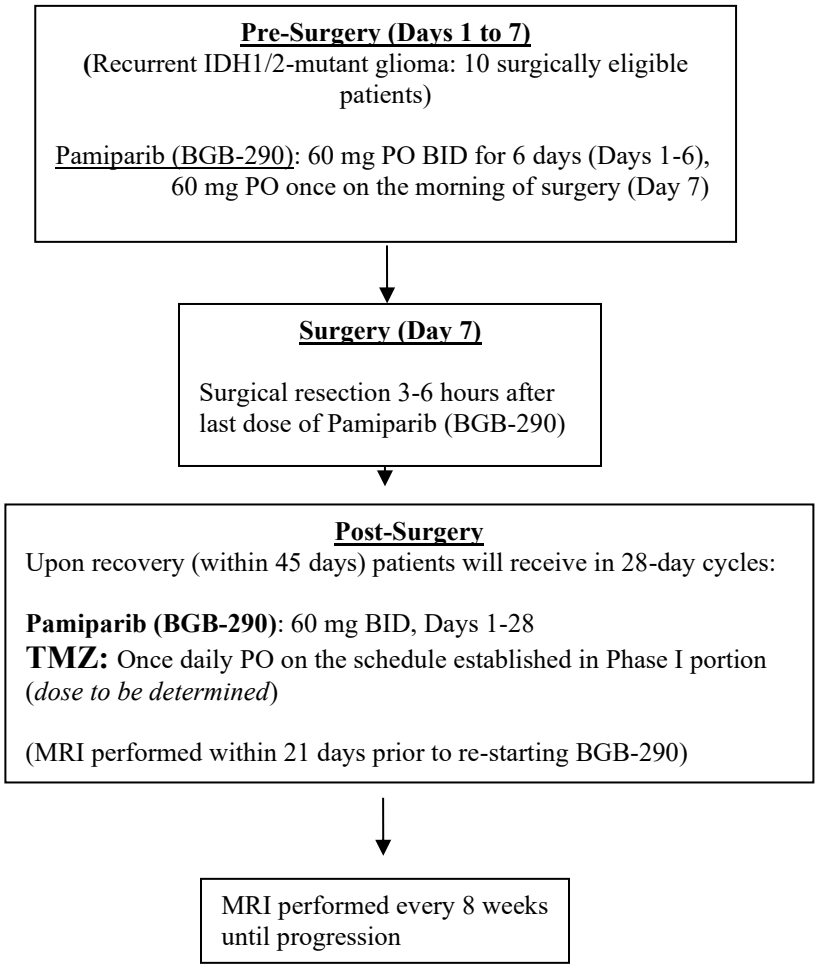
Pamiparib (BGB-290) will be given orally twice daily at 60 mg PO BID on Days 1 to 28 of 28-day cycles. TMZ 20 mg will be given orally once daily on the schedule established in the Phase I portion (*dose to be determined*).

Patients will be followed by routine blood work, general and neurological examination, and MR imaging. See Section 9.1 for schedule.

Patients may continue to receive cycles of pamiparib (BGB-290) until tumor progression, development of unacceptable toxicity, or meeting other criteria for going off treatment (Section 10.1). Patients will be followed for adverse events for at least 30 days after the last dose of pamiparib (BGB-290). All patients will be followed for survival.

4.3 Surgical Portion

Following completion of the Phase I portion, 10 patients with recurrent IDH1/2-mutant glioma (WHO grade II-IV) who are eligible for re-resection at the time of recurrence may be enrolled on a surgical portion of the study (pre-surgical cohort) and will receive pamiparib (BGB-290) 60 mg BID as a single agent for 7 days pre-surgery, including the day of surgery. At surgery fresh tumor tissue will be collected for correlative studies. Following recovery from surgery all patients will receive pamiparib (BGB-290) combined with TMZ post-operatively.



Patients should begin presurgical treatment with pamiparib (BGB-290) starting 6 days (Day 1) prior to the day of scheduled tumor resection (Day 7). Two additional days of dosing are permitted if unexpected logistical problems delay the surgery.

Doses of pamiparib (BGB-290) should be taken 12 hours apart ± 2 hours. On the day of surgery, the last pre-surgical dose must be taken 3-6 hours before surgery. The time that the dose is taken on the day of tumor resection must be recorded.

Blood samples for determining the concentration of drug in plasma will be collected from patients at baseline (prior to the first pre-surgical dose), on the day of surgery, immediately before the resection and immediately following the resection; see Section 9.5.2.

The tumor will be resected using neuronavigation or intraoperative MRI, enabling resection of enhancing tumor and resection or biopsy of non-enhancing tumor. Surgical resection of the non-enhancing lesions should be performed only in the non-eloquent areas that show FLAIR changes on MRI. Tissue may be collected from both the

enhancing core and non-enhancing edge of individual tumors. As a reminder, please refer to the Imaging Core Manual for further imaging requirements and submission information.

The concentration of pamiparib (BGB-290) will be determined in a 0.05-0.10 cm^3 (50-100 mg) section of tumor tissue obtained from a contrast enhancing and non-contrast enhancing region of the tumor. See Section 9.5.2.

Following surgery, all patients will continue with standard post-operative management.

Following recovery from surgical resection*, all patients will receive pamiparib (BGB-290) 60 mg BID in 28-day cycles combined with TMZ at the dose established in the Phase I portion (dose to be determined).

*Adequate recovery from surgical resection includes, but is not limited to, the following:

- No signs or symptoms of infections related to the surgical wound (*i.e.*, increasing erythema or cellulitis of the surrounding area, large amount of drainage, fever)
- Wound edges have healed

Post-operatively, patients must begin treatment within 45 days of surgical resection, and preferably within 3 weeks of the post-operative MRI; if more than 3 weeks elapse after the post-operative MRI, the patient will need a new MRI (please refer to the Imaging Core Manual for more information).

Patients will be followed by routine blood work, general and neurological examination, and MR imaging. See Section 9.1 for schedule.

Patients may continue to receive cycles of pamiparib (BGB-290) until tumor progression, development of unacceptable toxicity, or meeting other criteria for going off treatment (Section 10.1). Patients will be followed for adverse events for at least 30 days after the last dose of pamiparib (BGB-290). All patients will be followed for survival.

4.4 Treatment Requirements

All eligible patients who consent to this study must have a baseline (post-operative, if surgery is applicable) pre-treatment MRI (please refer to the Imaging Core Manual for more information). This baseline scan must be done within 21 days prior to the initiation of treatment.

Prior to every cycle patients must have:

1) ANC ≥ 1500/µl and platelets ≥ 100,000/µl.
AND
2) All toxicities recovered to ≤ grade 1 (or tolerable grade 2 for non-hematologic toxicity) or ≤ baseline.

4.5 Drug Administration

Phase I portion: To ensure accurate dose level and administration, all participating pharmacies must confirm dose levels with the ABTC Central Office. Please call 410-614-4400 to confirm the current dose level before preparing drug for administration.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be provided with medication diaries (Appendix I) and instructed in their use. Patients will be instructed to bring all unused medication and their diaries to each study visit for assessment of compliance.

4.5.1 Pamiparib (BGB-290) Administration

Pamiparib (BGB-290) capsules should be taken orally with 8 ounces of water. Patients are required to fast for at least one hour before and two hours after each dose of pamiparib (BGB-290). Capsules should be swallowed whole, not chewed or crushed.

Missed doses may be made up if taken within 2 hours after the scheduled administration time. Study drug may not be taken within 8 hours before the scheduled time for administration of the next dose. Patients who vomit after study drug administration should not retake that study drug dose but should resume taking study drug with the next scheduled dose.

Patients should record each dose of pamiparib (BGB-290) on the pamiparib (BGB-290) Patient Medication Diary in Appendix I.

Because Pamiparib (BGB-290) is intended for self-administration, if coming to the clinic presents a safety risk, it is permitted to ship the study drug and the appropriate medication diaries to the patient's residence before the scheduled cycle Day 1. The study drug should be shipped by a secure delivery method with package tracking and a delivery confirmation. The regulatory requirements for maintaining investigational product remain and should be addressed and documented.

Phase I:

Pamiparib (BGB-290) Dose: 60 mg BID

Pamiparib (BGB-290) will be administered twice daily continuously for each 28 day cycle. Each dose should be taken 12 hours apart (±2 hours), at approximately the same times each day.

Phase II:

Pamiparib (BGB-290) will be administered twice daily continuously for each 28 day cycle. Each dose should be taken 12 hours apart (±2 hours), at approximately the same times each day.

Surgical Portion:

Pre-surgery, pamiparib (BGB-290) will be administered twice daily for 6 days prior to scheduled surgery to remove tumor. Each dose should be taken 12 hours apart (±2 hours), at approximately the same times each day. A final presurgical dose should be taken the morning of surgery, 3-6 hours before the surgical procedure begins.

Post-surgery (upon recovery, within 45 days), pamiparib (BGB-290) will be administered at the dose established in the Phase I portion *(dose to be determined)* twice daily continuously for each 28 day cycle. Each dose should be taken 12 hours apart (±2 hours), at approximately the same times each day.

4.5.2 Temozolomide Administration

Temozolomide will be administered orally on an outpatient basis once a day for the number of days indicated by the assigned dose level in 28-day cycles. On the days that pamiparib (BGB-290) is also taken, TMZ should be taken at the same time as the morning dose of pamiparib (BGB-290).

Because Temozolomide is intended for self-administration, if coming to the clinic presents a safety risk, it is permitted to ship the study drug and the appropriate medication diaries to the patient's residence before the scheduled cycle Day 1. The study drug should be shipped by a secure delivery method with package tracking and a delivery confirmation. The regulatory requirements for maintaining investigational product remain and should be addressed and documented.

Phase I Starting Dose: The starting dose of TMZ for the first cohort of patients in the Phase I portion will be a flat dose of 20 mg/day.

Phase II and Surgical Arm (post-surgical treatment cycles): TMZ will be administered at the dose established in the Phase I portion *(dose to be determined)*.

Prior to each treatment cycle with temozolomide, a complete blood count (CBC) must be obtained (within -5 days prior to dosing). The start of all TMZ treatment cycles will be scheduled every 4 weeks (28 days, +3 days) after the first daily dose of temozolomide of the preceding treatment cycle.

If liver function tests (alkaline phosphatase, total bilirubin, SGOT, SGPT) are abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and

risks for the individual patient. For patients with significant liver function abnormalities, the benefits and risks of continuing treatment should be carefully considered.

Blood counts will be evaluated weekly. Within -5 days prior to first dose of each TMZ treatment cycle, the patient must have an ANC ≥ 1500/ul and platelet count ≥ 100,000/ul. On Day 1 of each cycle (within -5 days) all **non-hematological** toxicity grades 3 or 4 (except for alopecia, nausea and vomiting), related at least possibly to TMZ must have resolved (NCI Common Terminology Criteria for Adverse Events (CTCAE) grade ≤ 1). If toxicity persists, treatment should be delayed by one week for up to 3 consecutive weeks. If after 3 weeks of delay all toxicity has still not resolved then any further treatment with temozolomide should be stopped. See Section 5.2.

Capsules of temozolomide to be used in this study are available in 20 mg strengths. The dose administered should be recorded in the CRF.

Patients will be instructed to fast during at least one hour before and one hour after administration of temozolomide. Water is allowed during the fast period. Patients should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Missed doses should not be made up. A dose will be considered missed, and should not be made up, if more than 6 hours have passed from the time the dose is normally taken.

Antiemetic prophylaxis with a 5-HT_3-antagonist is strongly recommended.

4.6 General Concomitant Medication and Supportive Care Guidelines

Patients may receive other medications that the investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, anti-neoplastic biological therapy or other investigational agents. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study.

4.6.1 Prohibited/Restricted Concomitant Medications during Study

There must be a period of at least 10 days from discontinuation of prohibited drugs and initiation of therapy unless otherwise specified in the protocol. Requests for specific exceptions to the required wait time can be submitted to the ABTC Central Office by providing a pharmacological rationale that the washout period for a particular drug should be less than 10 days (or as specified in the protocol); this must be approved by the ABTC Central Office.

The primary metabolic pathway for pamiparib (BGB-290) involves the CYP3A isoform. The compounds/substances below are prohibited, as they are associated with possible interactions with pamiparib (BGB-290) through the CYP3A metabolic pathway, as well as other various metabolic interactions. Based on preliminary *in vitro* screening assays,

pamiparib (BGB-290) is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Investigators need to be aware that pamiparib (BGB-290) 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. Examples of these medications are also listed below, and these should be used cautiously with drug concentration monitoring where appropriate. In addition to CYP3A, pamiparib (BGB-290) can also be metabolized by CYP2C8 in human liver microsomes, but to a lesser extent. See below for medications that should be used with caution for the above reasons.

A handout with information for patients, their caregivers and non-study healthcare providers on possible interactions with other drugs and herbal supplements can be found in Appendix II, Patient Drug Information Handout and Wallet Card.

Prohibited Medications

The following medications and/or therapies should **not** be administered within the timeframes specified prior to enrollment and during the study:

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

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 38aradise fruit juice)
Herbal medications: Schisandra sphenanthera
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

Strong CYP3A Inducers:
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, firabutin, rifampin (rifampicin), St. John's wort (hypericumperforatum)

Medications to be used with caution
Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index:
Celecoxib
Phenytoin
Warfarin

Strong CYP2C8 Inhibitors:
Gemfibrozil

Herbal and Non-Traditional Medications

No data exist regarding the interaction of pamiparib (BGB-290) with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving pamiparib (BGB-290) therapy.

4.6.2 Anticonvulsants

No data exist regarding the interaction of pamiparib (BGB-290) with enzyme-inducing anti-epileptic drugs (EIAEDs). For this study, patients may **not** be on EIAEDs; patients who require anti-epileptic drugs (AED) may be on non-enzyme inducing anti-epileptic drugs (NEIAED). If a patient on this study protocol needs to have an AED started or needs to have a second AED added then only NEIAED should be used. There must be a ≥ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an EIAED drug must be used for a patient on study the patient will be removed from the protocol.

4.6.3 Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. The lowest required steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

4.6.4 Antiemetics

The use of any antiemetic deemed necessary for the care of the patient is allowed. The prophylactic use of a 5-HT3-antagonist or metoclopramide is strongly recommended before temozolomide administration.

5.0 DOSE MODIFICATION FOR TOXICITY

5.1 Dose Limiting Toxicity (DLT)

A DLT is defined as a clinically significant adverse event or abnormal laboratory value assessed as unrelated to disease progression, intercurrent illness, or concomitant medications and meets any of the criteria below. Any DLT must be a toxicity considered at least possibly related to pamiparib (BGB-290) or TMZ.

Dose limiting toxicities (treatment related) are defined below. Dose limiting toxicities must have an attribution of possible, probable, or definite to pamiparib (BGB-290) or TMZ. For patients experiencing a DLT, pamiparib (BGB-290) and TMZ will be stopped. If the patient recovers (≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline), refer to the Toxicity Management Table below for instruction on whether a dose reduction of TMZ or pamiparib (BGB-290) is required for subsequent doses, or whether pamiparib (BGB-290) and TMZ must be permanently discontinued. Skipped doses will not be made up. If there is any question or confusion concerning a DLT, the treating site should contact the ABTC Central Office to determine patient's DLT status. The ABTC Central Office, with the Study Chair, will make the final decision.

- Hematological toxicities will be considered dose limiting if any of the following occur and complete blood counts and differentials were obtained according to the mandated schedule (CBC, differential, and platelets drawn twice a week until the ANC ≥ 1500/μL and platelets ≥100,000/μL): grade 3 or 4 lymphopenia will not be considered a DLT.

    - Grade 4 Neutrophil count decreased (ANC of < 500/μL)
    - Grade 4 Platelet count decreased (Platelets < 25,000/μL)
    - Grade 3 or 4 Febrile neutropenia
    - Any hematological toxicity that prevents administration of > 80% of the planned TMZ doses for the first cycle

- Non-hematological toxicities will be considered dose limiting if any of the following occur:

    - Grades 3-4 seizure or intracranial hemorrhage
        - All other grade 3 neurologic toxicity (other than seizure/intracranial hemorrhage) responding ***within 3 days*** to steroids, anticonvulsants, or electrolyte correction will not be considered dose limiting.
    - Grades 3-4 severity with the following exceptions:
        - except nausea, vomiting, and diarrhea without sufficient prophylaxis ***lasting ≤3 days***;
        - except alopecia;
        - except grade 3 hyperglycemia;
        - except grade 3 electrolyte disturbances that are asymptomatic and that respond to replacement therapy ***within 3 days***;
        - A subject's first episode of deep venous thrombosis (DVT) or pulmonary embolism (PE) will not require dose modification (not a DLT).

ANY DLT (AS DEFINED ABOVE) CAUSING DELAY IN TREATMENT OF OVER 21 DAYS (OR OVER 14 DAYS FOR GRADE 3 HEPATIC TOXICITY) WITHOUT RECOVERY TO A ≤ GRADE 1 OR BASELINE STATUS WOULD RESULT IN TAKING THE PATIENT OFF TREATMENT.

5.2 Dose Delay and Dose Reduction

The dose levels and the approach to dose modification on this trial are shown below. Adverse events (AEs) should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented on the case report form.

Given the favorable safety profile of pamiparib (BGB-290), it is reasonable to assume that a Grade 3 or 4 toxicity is more likely to be due to the addition of TMZ to pamiparib (BGB-290) rather than pamiparib (BGB-290) on its own. Therefore, the decision of a dose reduction will affect TMZ first. Should TMZ dose reduction be insufficient to ensure tolerability of the combination regimen, dose reduction of pamiparib (BGB-290) from 60 mg to 40 mg or pamiparib (BGB-290)administered as a monotherapy may be discussed with the ABTC Central Office and the Study Chair.

If pamiparib (BGB-290) is permanently discontinued, the patient will be off treatment. If TMZ is permanently discontinued, the patient may continue pamiparib (BGB-290) if discussed with and approval is received from the study co-chairs.

Toxicity Management Table

Toxicity	***Actions***
Non-hematological toxicity	
Grade 3 Any other	Hold pamiparib (BGB-290) and TMZ until resolved to grade ≤1 or baseline and decrease TMZ by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4 Any other, with exception of fever	Permanently discontinue pamiparib (BGB-290) and TMZ.
Grade 3 Cardiac	Hold pamiparib (BGB-290) and TMZ until resolved to grade ≤1 or baseline and decrease TMZ by 1 dose level
Grade 4 Cardiac	Permanently discontinue pamiparib (BGB-290) and TMZ.
Prolonged QTc interval QTcF > 500 msec	Obtain triplicate ECGs (5 minutes apart) ~1 hour after initial ECG -If mean QTcF >500 ms, hold pamiparib (BGB-290) and TMZ until evaluation of ECGs by cardiologist -Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG -If mean QTcF >500 ms confirmed by cardiologist, permanently discontinue pamiparib (BGB-290) and TMZ

Toxicity	*Actions*
Grade 3 or 4 Pancreatitis	Permanently discontinue pamiparib (BGB-290) and TMZ
Grade 2 Hepatic (> 1.5-3 x ULN bilirubin) and Grade 3 Hepatic (> 3-10 x ULN bilirubin)	Hold pamiparib (BGB-290) and TMZ until recovery to grade ≤1 or baseline. -if resolved ≤ 7 days, then maintain dose levels -if resolved > 7 days, then decrease TMZ by 1 dose level
Grade 4 Hepatic (> 10 x ULN bilirubin)	Permanently discontinue pamiparib (BGB-290) and TMZ. Note: if grade 3 or 4 hyperbilirubinemia is due to indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out per institutional guidelines, then decrease TMZ by 1 dose level and continue treatment at the discretion of the investigator
Grade 3 Hepatic (> 5 and ≤ 20 x ULN AST and/or ALT)	Hold pamiparib (BGB-290) and TMZ until AST and/or ALT resolved to ≤ 5 x ULN or baseline. -if ≤ 5 x ULN within 14 days, then decrease pamiparib (BGB-290) and TMZ by 1 dose level -if second episode, permanently discontinue pamiparib (BGB-290) and TMZ -If persistent for > 14 days, permanently discontinue pamiparib (BGB-290) and TMZ
Grade 4 Hepatic (> 20 x ULN AST and/or ALT)	Permanently discontinue pamiparib (BGB-290) and TMZ.
Grade 3 Renal (> 3-6 x ULN serum creatinine) and Grade 4 Renal (> 6 x ULN serum creatinine)	Permanently discontinue pamiparib (BGB-290) and TMZ.
Serum creatinine 2-3 x ULN	Hold pamiparib (BGB-290) and TMZ until recovery to grade ≤1 or baseline. -if resolved ≤ 7 days, then maintain dose levels -if resolved > 7 days, then decrease TMZ by 1 dose level

Toxicity	*Actions*
Hematological toxicity	
Grade 3 Thrombocytopenia (platelets < 50,000 ≥ 25,000/μL)	Hold pamiparib (BGB-290) and TMZ until recovery to platelets ≥ 100000 μl or baseline. -if resolved ≤ 7 days, then maintain dose levels -if resolved > 7 days, then decrease TMZ by 1 dose level
Grade 4 Thrombocytopenia (platelets < 25,000/μL)	Hold pamiparib (BGB-290) and TMZ until resolved to platelets ≥ 100000 μl or baseline and decrease TMZ by 1 dose level
Grade 3 Neutropenia (neutrophils < 1,000 ≥ 500/μL)	Hold pamiparib (BGB-290) and TMZ until resolved to ≥ 1500/μl or baseline -if resolved ≤ 7 days, then maintain dose levels -if resolved > 7 days, then decrease TMZ by 1 dose level
Grade 4 Neutropenia (neutrophils < 500/μL)	Hold pamiparib (BGB-290) and TMZ until resolved to Grade ≤ 1 or baseline and decrease TMZ by 1 dose level
Febrile neutropenia (ANC < 1,000 with single temperature of > 38.3°C or sustained temperature of ≥ 38°C for > 1 hour)	Hold pamiparib (BGB-290) and TMZ until resolved and decrease TMZ by 1 dose level
Grade 2 Anemia (Hb < 10 - 8 g/dL)	First occurrence: continue dosing at current dose level. Second and subsequent occurrences: hold pamiparib (BGB-290) 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 (BGB-290) at same dose
Grade 3 Anemia (Hb < 8 g/dL)	Hold pamiparib (BGB-290) and TMZ until resolved to Grade ≤ 1 or baseline -if resolved ≤ 7 days, then maintain dose levels -if resolved > 7 days, then decrease TMZ by 1 dose level

Toxicity	*Actions*
Grade 4 Anemia (life threatening consequences; urgent intervention indicated)	Hold pamiparib (BGB-290) and TMZ until resolved to Grade ≤ 1 or baseline and decrease TMZ by 1 dose level

5.2.1 Dose Modification for Temozolomide and Pamiparib (BGB-290)

Dose reductions are required as indicated in the toxicity table above for any dose limiting toxicity (as defined in Section 5.1). Dosing will stop until the DLT has resolved to ≤ grade 1 [or tolerable grade 2 for non-hematologic toxicity] or ≤ baseline. The maximum length of time that pamiparib (BGB-290) and TMZ can be held is 21 days, or as stipulated in the table. After resolution, the dose of TMZ will be modified as stipulated below, with a maximum of 2 dose reductions. If treatment-related toxicity is not resolved in ≤ 21 days (or as stipulated), the patient will be considered for monotherapy with pamiparib (BGB-290). If there is any question, the ABTC Central Office and the study chair should be contacted.

TMZ Dose Reduction Schedule

Dose level	Temozolomide dose	Dose reduction 1	Dose reduction 2
1 (starting dose)	20 mg QD Days 1-28	20 mg QD Days 1-21	20 mg QD Days 1-14
-1	20 mg QD Days 1-21	20 mg QD Days 1-14	20 mg QD Days 1-7
-2	20 mg QD Days 1-14	20 mg QD Days 1-7	Either off study or pamiparib (BGB-290) alone
-3	20 mg QD Days 1-7	Either off study or pamiparib (BGB-290) alone	N/A

Blood counts will be evaluated weekly. Within -5 days prior to first dose of each cycle the patient must have an ANC ≥ 1500/ul and platelet count ≥ 100,000/ul. On Day 1 of each cycle (within -5 days) all **non-hematological** toxicity grade 3 or 4 (except for alopecia, nausea and vomiting) must have resolved (CTCAE grade ≤ 1). If toxicity persists, treatment should be delayed by one week for up to 3 consecutive weeks. If after 3 weeks of delay all toxicity has still not resolved then any further treatment with temozolomide should be stopped (patient is off treatment).

If pamiparib (BGB-290) must be modified as stipulated in the Toxicity Management Table, the dose of pamiparib (BGB-290) will be modified as shown below, with a maximum of 2 dose reductions.

Pamiparib (BGB-290) Dose Reduction Schedule

Dose Level	Pamiparib (BGB-290)
Starting dose	60 mg b.i.d.
First dose reduction	40 mg b.i.d.
Second dose reduction	20 mg b.i.d.

5.3 Major Events

Major events are non-treatment-related grade 3 or 4 hematologic and non-hematologic adverse events. Treatment should be delayed for major events if pamiparib (BGB-290) may further complicate the non-treatment-related event. If a major event requires a delay of treatment, treatment must be delayed until the event is resolved (≤ grade 1 or ≤ baseline). If the event is not resolved in ≤ 28 days, the patient will be removed from treatment. The ABTC Central Office should be consulted if you are not clear on whether to continue or delay treatment.

5.4 Use of Hematologic Growth Factors

No growth factors (G-CSF or GM-CSF) are to be used prophylactically in this protocol. Clinicians caring for patients on this protocol are permitted to use these growth factors to provide optimal care for patients with severe neutropenia in accordance with the ASCO guidelines, (JCO, 12, 1994: pp2471-2508). If these growth factors are used in the acute setting of neutropenia and infection (documented or suspected), they will not be utilized prophylactically in subsequent cycles and they will not subsequently be used *in lieu* of dose reduction of pamiparib (BGB-290) or TMZ.

5.5 Toxicity Criteria

All toxicities will be described and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). See also Section 9.2.1, Recording of Adverse Events.

6.0 PHARMACEUTICAL INFORMATION

6.1 Pamiparib (BGB-290) (NSC# 803412)

Chemical Name: (R)-2-fluoro-10a-methyl-5,8,9,10,10a,11-hexahydro-5,6,7a,11-tetraazyacyclohepta[def]cyclopenta[a]fluoren-4(7H)-one

Molecular Formula: $C_{16}H_{15}FN_4O$

Molecular Mass: **298**

Mode of Action: highly potent and selective PARP inhibitor, binds to PARP enzyme and prevents PARP-mediated repair of single-stranded DNA breaks via base-excision repair, thus enhancing the accumulation of DNA double strand breaks.

How Supplied: supplied by BeiGene Ltd. pamiparib (BGB-290) pellet-in-capsules are provided in a container with a child-resistant closure. Each container is labeled with space to enter the subject's ID, treatment and period number. The label is pre-printed and includes content and quantity of pamiparib (BGB-290), protocol number, batch number, administration instructions, storage instructions and expiry date. Subjects will receive pamiparib (BGB-290) as 10 mg, 20 mg or 40 mg capsules, depending on dose level and availability.

Storage: Pamiparib (BGB-290) must be kept at 15°C to 30°C. An accurate study drug accountability log must be maintained and kept up to date at all times.

Stability: Pamiparib (BGB-290) is an oral formulation. The drug should be stable at minimum until the expiration date on the bottle.

Route of Administration: Pamiparib (BGB-290) is taken by mouth with 8 ounces of water while fasting.

Known Potential Drug Interactions: Strong and moderate CYP3A inhibitors and strong CYP3A inducers are prohibited due to potential for drug interactions. Strong CYP2C8 inhibitors and sensitive CYP2C9 substrates or CYP2C9 substrates with narrow therapeutic index should be used with caution.

Contraindications: Pamiparib (BGB-290) should not be used in patients who are pregnant.

6.1.1 Agent Ordering

Pamiparib (BGB-290) may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF).

Once a site has submitted all required regulatory documents to ABTC and BeiGene (Form 1572, curriculum vitae, licenses, IRB approval of protocol and consent), an initial supply of drug can be ordered. An ABTC drug order form, which can be found on the ABTC website (ABTConsortium.org), should be emailed to the ABTC Central Office to initiate sending of the drug. The ABTC Central Office will forward the drug order form to BeiGene. Please allow 7 days from the receipt of the drug order form at BeiGene for drug shipment.

6.1.2 Agent Accountability

Each institutional Investigator, or a responsible party designated by the Investigator, agrees to supply drugs only to those subjects enrolled in the study and must maintain a careful record of the inventory and disposition of all drugs received from BeiGene, using the NCI Investigational Drug Accountability Record Form. Upon termination of the study, the

Investigator or designee must complete a final inventory of supplies.

6.2 Temozolomide

Generic name:	Temozolomide
Commercial name:	Temodar®
Chemical name:	3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8 carboxamide
Classification	Antineoplastic agent, alkylating
Molecular Formula:	$C_6H_6N_6O_2$
Molecular Weight:	194.15
Mechanism of Action:	Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.
Appearance:	White to light tan/light pink powder
Melting point:	Decomposes at 206ºC
How Supplied:	Commercially available
Stability:	The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH. The product label recommends Storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
Half life:	Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours

Packaging, Dispensing and Storage

Temozolomide capsules are available in 5-mg, 20-mg, and 100-mg, strengths. The capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. The 5-mg, 20-mg, 100-mg capsule strengths are available in 5-count and 14-count packages. The product label recommends Storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Labeling of the packages containing the capsules will be done in accordance with the local procedures (as required by law). According to the dosing the hospital pharmacist delivers the temozolomide dosage for a complete cycle to the subject.

7.0 PROCEDURES FOR PATIENT ENTRY ON STUDY

This study is supported by the NCI Cancer Trials Support Unit (CTSU) Regulatory Office and uses the Oncology Patient Enrollment Network (OPEN).

7.1 CTEP Registration Procedures

Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN) or Rave or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

7.2 Site Registration Requirements – Institutional Review Board Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Requirements For ABTC-1801 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

7.3 Patient Registration

Patient enrollment will be facilitated using OPEN. All site staff will use OPEN. OPEN is a web-based registration system available for ABTC studies from 9 a.m. to 4:30 p.m. Eastern Time. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Since this study includes a Phase I component, patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the registration system on OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot- reservation confirmation is obtained, site staff may then proceed to enroll patients to this study.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for credentialing in the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role (or equivalent) on the relevant Group or CTSU roster.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Upon completion of the registration process in OPEN, sites must contact the ABTC Central Office to obtain confirmation of the patient's registration and dose assignment. The local investigational pharmacy should call the ABTC Central Office to confirm the actual dose prior to dispensing the first dose of the first cycle. **No patient may begin treatment until registration AND dose have been confirmed by the ABTC Central Office.**

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL (https://open.ctsu.org). For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

8.0 Response Assessment / Safety and Quality Assurance

8.1 Criteria for Response Assessment

Patients with measurable enhancing disease will be assessed by the high grade glioma (HGG) RANO (radiographic assessment in neuro-oncology) criteria[64], while patients with only T2/FLAIR abnormalities will be assessed by the low grade glioma (LGG) RANO criteria[63.] For the purposes of this study, subjects should be re-evaluated at the end of every 2 cycles (approximately every 8 weeks) with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below. As a reminder, all assessments should be in compliance with the Imaging Core Manual.

Measurable disease. Bi-dimensionally, contrast-enhancing, measurable lesions with clearly defined margins by MRI scan, with a minimal size of 1 cm x 1 cm, and visible on 2 axial slices which are at least 5 mm apart with 0 mm skip. Measurement of tumor around a cyst or surgical cavity, if necessary, requires a minimum thickness of 3 mm. If there are >2 lesions (multifocal) at baseline, the investigator must choose the largest two to be followed before a participant is entered on study. The remaining lesions will be considered non-measureable for the purpose of objective response determination. Unless progression is observed, objective response can only be determined when all measurable and non-measurable lesions are assessed.

8.1.1 HGG RANO

Complete Response – CR (requires *all* of the following):

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No new lesions.
c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
d) Subjects must be off corticosteroids (or on physiologic replacement doses only).
e) Stable or improved non-enhancing (T2/FLAIR) lesions.
f) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response – PR (requires *all* of the following):

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
b) No progression of non-measurable disease.
c) No new lesions.
d) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.
e) The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.
f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.
g) Stable or improved clinically.

Note: Subjects with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease – SD (requires *all* of the following):

a) Does not qualify for CR, PR, or progressive disease (PD).
b) The designation of stable disease requires a minimum of 4-week duration.
c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.
d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in

corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
e) Stable clinically.

Progressive Disease – PD (defined by *any* of the following):

a) ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids.*
b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy,* not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).
c) Any new lesion.
d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose. The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.
e) Failure to return for evaluation due to death or deteriorating condition.
f) Clear progression of non-measurable disease.

* Stable doses of corticosteroids include patients not on corticosteroids.

8.1.2 LGG RANO

Complete Response – CR (requires *all* of the following):

a) Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely);
b) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement;
c) patients must be off corticosteroids or only on physiological replacement doses;
d) patients should be stable or improved clinically

Partial Response – PR (requires *all* of the following compared with the baseline scan):

a) greater than or equal to 50% decrease in the product of perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks compared with baseline;
b) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement;
c) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Minor Response – MR (requires *all* of the following):

a) a decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared with baseline;
b) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement;
c) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Stable Disease – SD (requires *all* of the following):

a) does not qualify for complete, partial, or minor response, or progression
b) stable area of non-enhancing abnormalities on T2 or FLAIR imaging;
c) no new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement; and
d) patients should be on a corticosteroid dose that should not be greater than the dose at time of baseline scan, and should be stable or improved clinically

Progressive Disease – PD (defined by *any* of the following):

a) development of new lesions or increase of enhancement (radiological evidence of malignant transformation);
b) a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events;
c) definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose;
d) failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorder

8.2 Assessment of Response

Assessment of response will begin with the MRI performed just prior to *every odd-numbered* treatment cycle. If during any scheduled MRI, the subject has a Complete Response or Partial Response, the MRI should be repeated prior to the next cycle. All scans are to be compared to the smallest measurement scan to date. The subject will then return to the every odd-numbered cycle schedule. This is required to confirm the duration of response. Subjects will be classified as responders if they have a minimum duration of response for 4 weeks at any time after the first cycle of pamiparib (BGB-290). MRI scans of subjects showing tumor response will be centrally reviewed by a neuroradiologist who will independently assess tumor size and compute percent tumor regression. As a reminder, all assessments should be in compliance with the Imaging Core Manual.

8.3 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry, pregnancy testing (in women of childbearing potential), regular measurement of vital signs, and the performance of physical/neurological examinations; ECGs and other cardiac monitoring may be performed as necessary.

Monitoring Pregnancy

Pregnancy in itself is not regarded as an AE or SAE, however all reports of congenital abnormalities/birth defects, elective terminations for medical reasons and any serious complications of pregnancy (including spontaneous miscarriage, still birth and blighted ovum) should be reported as SAEs.

In the event of any occurrence of pregnancy in a patient or the female partner of a male patient, the site will complete and submit (via email of fax) the Pregnancy Notification Report (Appendix 5) within 24 hours of awareness. All pregnancy follow-up information should be sent to COV PV using the Pregnancy Follow-up Report (Appendix 6). Pregnancy Appendix 5 and 6 can be found at the ABTC Consortium Website www.abtconsortium.org

Monitoring of the patient should continue until conclusion of the pregnancy. The outcome of all pregnancies (live birth, spontaneous miscarriage, elective termination, or congenital abnormality/birth defects) must be followed up and documented, including patients who have discontinued the study, provided that the patient/partner provides consent. In addition, information about the pregnancy, the birth of the baby, and the health of the baby for up to 8 weeks after birth, even after study treatment has stopped, should be collected.

A female study participant who becomes pregnant must be withdrawn from the study; however, male study participants whose partner becomes pregnant can remain in the study.

Pregnancy cases will be followed-up every 3 months until final pregnancy outcome has been provided and a request for the outcome will also be issued within two weeks of the anticipated delivery date. Pregnancy reports will be tracked on a separate tab of the SAE tracker.

8.4 Quality Assurance

Neuropathology: The neuropathologic diagnosis of glioblastoma will be made at the respective institution. If any question arises regarding the accuracy of the neuropathologic diagnosis, slides (and pathological blocks, if necessary) will be reviewed by the central review pathologist. For protocols with “response” as an outcome, all patients with a

documented complete response or partial response may have representative pathology slides undergo central review.

Neuroradiology: MRI scans of patients showing tumor response as assessed locally will be centrally reviewed by the ABTC Imaging Core at the UCLA Brain Tumor Imaging Laboratory by board-certified neuroradiologists who will independently assess tumor size and assess radiographic response. Volumetric growth rates will be assessed by first performing volumetric (3D) contouring of the T2/FLAIR hyperintense lesion on historic (pre-treatment) and on-study scans by an imaging technologist. These segmentations will then be signed off by board-certified neuroradiologists prior to calculation of growth rates. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

Adherence to protocol therapy: Screening/baseline source documentation will be submitted/uploaded into CTEP's iMedidata Rave system and will be reviewed by the ABTC Central Office. As a quality assurance measure for the treatment delivered on this protocol, primary patient records may be reviewed. The records to be examined will be selected retrospectively and at random; complete records must therefore be maintained on each patient treated on the protocol. These records should include primary documentation (e.g., laboratory report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.), which confirm that:

- The patient met each eligibility criterion.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given; any reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (MRI scan, lab reports, dated notes on measurements and clinical assessment, as appropriate).
- NCI Drug Accountability Records were maintained for this protocol.

9.0 MONITORING OF PATIENTS

9.1 Tables of Required Observations

9.1.1 Phase I and Phase II (28-Day Cycles)

	Baseline	Days 1-28 of every cycle	Weekly During All Cycles	Pre-Odd Cycles (cycles 3+)	Pre-Even Cycles	Off Treatment	30 Days post-last dose
Pamiparib (BGB-290)		6					
Temozolomide		7					
AE Evaluation	1			5	5	8,10	11
Glucocorticoids Dose Evaluation	1			5		8	
MRI	1			5		8	
H&P/Neuro Exam	1			5	5	8	
KPS	1			5	5	8	
Vital Signs	1,2			2,5	2,5	2,8	
CBC, Diff, Platelets	1		9,13,15	5,9	5,9	8	
Serum Chemistry	1,3			3,5	3,5	3,8	
APTT or PTT	1						
Serum Pregnancy Test	14,4						
Urine Pregnancy Test				4,5	4,5	4	
Archived Tumor Tissue	12						

1– All baseline measurements must be done within minus 21 calendar days of treatment administration unless otherwise specified.

2– Including blood pressure, respiratory rate, heart rate, temperature, weight, height: height is required at baseline only; weight is required at pre-odd cycle evaluations only. Patients with dyspnea or asymptomatic desaturation (oxygen saturation <92%), will be further evaluated as clinically indicated: evaluation may include chest x-ray, arterial blood gas analysis, pulmonary function testing including diffusion capacity, co-oximetry, as well as evaluation for specific causes of hypoxia/dyspnea.

3– Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.

4– For women of child-bearing potential: monthly pregnancy tests through 6 months after completion of pamiparib (BGB-290) or temozolomide administration.

5– Within minus 5 calendar days of cycle start.

6– Pamiparib (BGB-290) is administered orally twice daily on Days 1-28 of each 28-day cycle (see Section 4.5.1). Patients are required to keep a medication diary.

7– TMZ is administered orally once daily according to the specified dose level of each 28-day cycle (see Section 4.5.2). Patients are required to keep a medication diary.

8– Evaluations done within +7 days of off treatment date unless indicated: do not repeat: if MRI within minus 14 days of off-treatment date (please refer to the Imaging Core Manual for further imaging requirements and submission information) ; if H&P/neuro, KPS, labs within minus 5 days of off-treatment date.

9– If ANC < 1500 or plts < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥1500 or plts ≥100,000) per protocol. If counts are recovered (ANC ≥1500 or plts ≥100,000) on day of scheduled drawing do not repeat until next protocol schedule day

10 – Adverse Events must be followed for at least 30 days from last dose of pamiparib (BGB-290).

11– Perform within +14 days of the 30-day post-last dose date.

12– Archived tumor tissue from a prior resection for glioma, preferably from the initial diagnosis, will be collected from all patients. See Section 9.5.1.

13– ± 1 day

14-Perform within minus 7 days of first dose

15- In subjects whose CBC, Diff, Platelets have been stable through the first 6 cycles, the frequency of hematologic testing can be reduced to a q2 weeks schedule (Day 15 of every cycle and Pre-cycle evaluation) starting in Cycle 7. CBC, Diff, Platelets will be considered "stable" if the following criteria are met: 1) No reports of ANC<1500/µl in ANY of the Cycles 1-6 weekly Labs and 2) No reports of Platelets<100,000/µl in ANY of the Cycles 1-6 weekly Labs. If at any point during treatment on the revised q2 weeks schedule the above mentioned ANC and Platelets criteria are not met, CBC, Diff, Platelets should be repeated twice a week until counts are recovered (ANC ≥1500 or Platelets ≥100,000). Once counts are recovered, the schedule of CBC, Diff, Platelets should go back to, and stay at, weekly monitoring (NOT q2 weeks).

IMPORTANT: *The guidance below is subject to applicable local Institutional Policy on telemedicine. In the event that local Institutional Policy regarding telemedicine differs from this guidance, then please follow local Institutional Policy.*

Telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Additionally, informed consent should be obtained in person, but if deemed necessary, via telemedicine.

9.1.2 Surgical Portion (includes pre-surgical dosing)

	Baseline	Pre-Surgery	Day of Surgery	Post-Surgery	Post-Surgery Cycles	Weekly During All Cycles	Pre-Odd Cycles	Pre-Even Cycles	Off Treat-ment	30 Days post-last dose
Pamiparib (BGB-290)		6	6		6					
Temozolomide					7					
AE Evaluation	1		15	16			5	5	8,10	11
Glucocorticoids Dose Evaluation	1			16			5		8	
MRI	1			16			5		8	
H&P/Neuro Exam	1						5	5	8	
KPS	1						5	5	8	
Vital Signs	1,2						2,5	2,5	2,8	
CBC, Diff, Platelets	1					9,18,19	5,9	5,9	8	
Serum Chemistry	1,3						3,5	3,5	3,8	
APTT or PTT	1									
Serum Pregnancy Test	4,17									
Urine Pregnancy Test							4,5	4,5	4	
Archived Tumor Tissue	12									
Blood Samples for Pharmacokinetics	13		13							
Fresh Tumor Tissue			14							

1– All baseline measurements must be done within minus 21 calendar days of treatment administration unless otherwise specified.
2– Including blood pressure, respiratory rate, heart rate, temperature, weight, height: height is required at baseline only; weight is required at pre-odd cycle evaluations only.
3– Including albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, magnesium, phosphorus, potassium, SGOT, SGPT, sodium.
4– For women of child-bearing potential: monthly pregnancy tests through 6 months after completion of pamiparib (BGB-290) or temozolomide administration.
5– Within minus 5 calendar days of cycle start including Pre-Cycle 1. MRI does not need to be repeated if post-surgical MRI is within 21 days of Cycle 1 start. Please refer to the Imaging Core Manual for further imaging requirements and submission information.
6– Pre-surgery pamiparib (BGB-290) is administered twice daily for 7-9 days prior to scheduled surgery, including the day of surgery;
Post-surgery pamiparib (BGB-290) is administered orally twice daily on Days 1-28 of each 28-day cycle. See Section 4.5.1. Patients are required to keep a medication diary. Patients are required to keep a medication diary.
7– Post-surgery, temozolomide is administered once daily on according to the specified dose level of each 28-day cycle. See Section 4.5.2.
8– Evaluations done within +7 days of off treatment date unless indicated: do not repeat: if MRI within minus 14 days of off-treatment date (please refer to the Imaging Core Manual for further imaging requirements and submission information).; if H&P/neuro, KPS, labs within minus 5 days of off-treatment date.
9– If ANC < 1500 or plts < 100,000, CBCs/differentials will be repeated twice a week until counts are recovered (ANC ≥1500 or plts ≥100,000) per protocol. If counts are recovered (ANC ≥1500 or plts ≥100,000) on day of scheduled drawing do not repeat until next protocol schedule day
10– Adverse Events must be followed for at least 30 days from last dose of pamiparib (BGB-290).
11– Perform within +14 days of the 30-day post-last dose date.
12– Archived tumor tissue from a prior resection for glioma, preferably from the initial diagnosis, will be collected from patients. See Section 9.5.1.
13– Blood samples will be obtained for pharmacokinetics at baseline (prior to first pre-surgical dose), and shortly before and after surgical resection. Section 9.5.2.
14–Fresh tumor tissue for drug concentration will be collected day of surgery. See Sections 9.5.2.
15– Patient should be seen on the day of surgery (prior to surgery) to evaluate for AEs.
16– Within 3 days post-surgery.
17- Perform within minus 7 days of first dose.
18-± 1 day
19- In subjects whose CBC, Diff, Platelets have been stable through the first 6 cycles, the frequency of hematologic testing can be reduced to a q2 weeks schedule (Day 15 of every cycle and Pre-cycle evaluation) starting in Cycle 7. CBC, Diff, Platelets will be considered "stable" if the following criteria are met: 1) No reports of ANC<1500/µl in ANY of the Cycles 1-6 weekly Labs and 2) No reports of Platelets<100,000/µl in ANY of the Cycles 1-6 weekly Labs. If at any point during treatment on the revised q2 weeks schedule the above mentioned ANC and Platelets criteria are not met, CBC, Diff, Platelets should be repeated twice a week until counts are recovered (ANC ≥1500 or Platelets ≥100,000). Once counts are recovered, the schedule of CBC, Diff, Platelets should go back to, and stay at, weekly monitoring (NOT q2 weeks).

IMPORTANT: *The guidance below is subject to applicable local Institutional Policy on telemedicine. In the event that local Institutional Policy regarding telemedicine differs from this guidance, then please follow local Institutional Policy.*

Telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

Additionally, informed consent should be obtained in person, but if deemed necessary, via telemedicine.

9.2 Adverse Events

Patients will be evaluated for safety if they have received at least one dose of pamiparib (BGB-290).

The timely reporting of AEs (including deaths) is required by the U.S. Food and Drug Administration. The reporting of toxicities is part of the data reporting for this study. Adverse events will be collected for at least 30 days following the last dose of study drug. Beyond this time point only newly occurring adverse events that are serious and drug-related will be recorded.

Adverse events must be reported to the ABTC Central Office and the NCI by the investigative site in the manner described and per the requirements of the clinical site's IRB.

Adverse events will be entered into CTEP's iMedidata Rave database by the investigative site in a timely manner. See Section – Data Collection/Reporting.

9.2.1 Adverse Events and Potential Risks

9.2.1.1 Adverse Events and Potential Risks with Pamiparib (BGB-290) in combination with Temozolomide

As of 18 June 2021, a total of 208 patients have received pamiparib with temozolomide. The most common pamiparib and/or temozolomide side effects reported by these patients are listed below. In most patients, the side effects were mild and responded to treatment. In some patients, the side effects were long-lasting, serious, or required urgent treatment. Some side effects may be life-threatening or fatal.

The side effects are adapted from Section 5.2.5.2 (Treatment-Emergent Adverse Events Assessed as Related to Study Treatment) for the pamiparib plus TMZ combination pool in the Pamiparib Investigator's Brochure (IB) Edition 7. The term "side effect" implies causality.

Adverse Drug Reactions

See the Informed Consent and Investigator Brochure for the risk tables.

9.2.1.2 Known Potential Toxicities of Temozolomide

Known potential toxicities of temozolomide are hematological toxicities (leucopenia, lymphopenia, thrombocytopenia, and anemia), renal insufficiency, nausea and vomiting, liver enzyme abnormalities, lethargy, rash, headache, alopecia, constipation, fatigue/malaise, anorexia, hyperglycemia and diarrhea are known toxicities. Recently, cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that

liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. Refer to the package insert for additional information on adverse events observed to date.

Rats given temozolomide in recent multidose toxicity studies have developed adenocarcinoma of the breast, fibrosarcomas, malignant Schwannomas (a variant of fibrosarcoma), keratoacanthomas and basal cell adenomas. Similar studies conducted in dogs did not reveal any similar findings. The significance of this finding for humans is not known presently.

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and subjects. Subjects with known or suspected hypersensitivity to temozolomide should not be treated with temozolomide. There are no data available on the effect or management of temozolomide overdose.

Additional information is available in the temozolomide package insert (www.temodar.com)

9.2.2 Adverse Event Characteristics

Definition - Adverse Event (AE)

Adverse event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

Recording of Adverse Events - ABTC AE Form

- The investigator will monitor each patient closely for the development of adverse events and record all such events on the ABTC AE Case Report Form. Each single sign or symptom must be reported separately.

- **CTCAE term (AE description) and grade**: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). You must use one of the CTCAE criteria to define your event.

  Adverse events not included in the CTCAE should be reported under "Other" within the appropriate category and graded 1 to 5 according to the general grade definitions - mild, moderate, severe, life-threatening, fatal or disabling - as provided in the CTCAE or the CTCAE Manual. New adverse events may be submitted to the CTEP Help Desk at ncictcaehelp@mail.nih.gov for annual evaluation by the CTCAE Change Management Committee.

- **Attribution of the AE:** The investigator will be asked to document his/her opinion of the relationship of the event to study medication as follows:

  - *Unrelated* – The AE is clearly not related to the investigational agent(s).
  - *Unlikely* – The AE is doubtfully related to the investigational agent(s).
  - *Possible* – The AE may be related to the investigational agent(s).
  - *Probable* – The AE is most likely related to the investigational agent(s).
  - *Definite* – The AE is clearly related to the investigational agent(s).

- All adverse events should be followed up in accordance with good medical practice. Abnormalities of laboratory events which, in the opinion of the investigator, constitute adverse events (even if not serious) should be followed.

9.3 Serious Adverse Events and Expedited Adverse Event Reporting

9.3.1 Definition – Serious Adverse Event (SAE)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.3.2 Expedited Adverse Event Reporting

- **Use CTEP-AERS Web Application and Document on ABTC AE Form**

  - All SAEs must be documented on both the ABTC AE form and using the CTEP-AERS Web Application within 24 hours of learning of the event.

  - Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers). In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to the ABTC Central Office by telephone at 410-614-4400 or 410-955-3657 or 410-599-4610. Once Internet connectivity is restored, the 24-hour notification must be entered electronically into CTEP-AERS by the original submitter at the site.

- ABTC will be notified automatically when an SAE is reported through CTEP-AERS (within 24 hours). All SAEs will be documented and tracked by the ABTC Central Office. Queries and follow up required for completing all SAEs will be conducted through the ABTC Central Office in a timely fashion. When an expedited report is required (7 or 15 days), a speedy resolution of queries will be expected in order to allow for on-time reporting to the FDA. BeiGene is responsible for reporting all applicable SAEs to the FDA.

- CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) of the Adult Brain Tumor Consortium (ABTC), the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

- The ABTC Central Office is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

- Expedited Reporting Guidelines

  Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

  Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

  Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

9.3.3 Other SAE Reporting

Any Serious Adverse Event, as described in Section 9.3.1, including death due to any cause, which occurs during this study must be **reported immediately (within 24 hours)** to the ABTC Central Office.

A phone call must be made to:

SERENA DESIDERI
ABTC DATA COORDINATOR
OFFICE: 410-614-4400
FAX: 410-367-3208

OR JOY FISHER, ABTC MANAGER: 410-955-3657 / 410-599-4610

These events also must be reported by the investigator to the appropriate Institutional Review Board (IRB).

Patients who are removed from study due to adverse events should be followed until the adverse event has resolved or stabilized. Copies of relevant documentation, such as laboratory reports, should be kept with the patient's study records.

Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

Any secondary malignancies that occur following treatment with pamiparib (BGB-290) should be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in Section 12.0.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

9.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions (Section 12.4).**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

9.5 Correlative Studies

Exploratory biomarker and correlative studies are focused on identifying key molecular correlates of treatment response. A subset of patients will be accrued to a surgical component of the study in which pamiparib (BGB-290) is administered prior to re-resection to assess intra-tumoral drug levels.

30 unstained FFPE slides are required for all patients enrolled on this study, typically from the initial diagnosis specimen. Exceptions will be made in cases where there is limited tissue, upon approval by the study Chairs. All samples, including blood and tissue, will be sent to the Bindra laboratory for distribution to the study collaborators.

9.5.1 Archival Tumor Tissue (all patients)

2HG Quantification

Quantification of 2HG in archival FFPE specimens via LC-MS detection and correlation with treatment response will be performed in collaboration with Jing Li, PhD (Pharmacology Core, Karmanos Cancer Institute [KCI], Wayne State University School of Medicine), using optimized protocols developed by Li and Bindra.

Response Correlation with 2HG, Somatic Alterations, Gene Expression/Methylation Patterns

Response correlation with 2HG, somatic alterations, and gene expression/methylation patterns in FFPE tumor tissue will be performed in collaboration with the Translational Genomics Research Institute (TGen). TGen investigators have participated in the initial TCGA efforts to sequence glioblastoma [33]. Subsequently, prospective precision medicine trials in recurrent adult GBM (NCT02060890) and pediatric DIPG (NCT02274987) demonstrate core competencies to support correlative trials. Sequencing pipelines developed at TGen have also been utilized for identification of genomic signatures of vulnerability in adult GBM patients via a retrospective analysis [34].

Archival FFPE Slide Preparation and Shipping Requirements:

Each submitting institution should submit 30 unstained sections from a previous surgery for glioma, preferably the initial diagnosis specimen, 5 microns thick, mounted on standard glass microscope slides.

Tissue Specimens should be mailed according to these instructions:

1. Label the samples with the following information:

   ABTC Protocol Number (ABTC 1801)
   Description (FFPE slides)
   Patient Study ID Number
   Date of Collection
   Time of Collection

2. Complete the "shipping manifest for research specimen collection and shipping" (see SOP/Lab Manual)
3. Place the FFPE slides in a plastic zip lock bag and wrap in bubble wrap or another type of padded material prior to shipping. The zip lock bag can be placed into a FedEx envelope or small shipping box.
4. Verify that the FedEx air bill is marked Standard Overnight Shipping.
5. Call Courier Service to pick up specimens.
6. Ship overnight (Mon-Thur). No shipments will occur over weekends or holidays. Prior to any shipment, please notify Dr. Ranjit Bindra via email and/or telephone. The samples will be shipped to the following address:

   Laboratory of Dr. Ranjit Bindra
   c/o Ranjini Sundaram
   Yale University School of Medicine
   15 York, HRT205
   New Haven, CT 06520
   Email: ranjit.bindra@yale.edu

9.5.2 Brain Tissue Concentrations and Plasma Pharmacokinetics (Surgical Portion)

Tumor tissue pamiparib (BGB-290) levels, 2HG, and PARylation will be assessed in a patient subset treated with drug prior to re-resection (Surgical Portion), using optimized protocols in the Li group as noted in Section 9.5.1, and also based on methodology developed and validated in the Bindra laboratory.

Blood samples for pharmacokinetics will be drawn at baseline (prior to first pre-surgical dose) and immediately before and after surgery. The PK sample drawn immediately before surgery must be taken following the Day 7 dose (which is taken 3-6 hours prior to surgery).

The concentration of pamiparib (BGB-290) will be determined in a 0.05-0.10 cm^3 (50-100 mg) section of tumor tissue obtained from a contrast enhancing and non-contrast enhancing region of the tumor. Doses of pamiparib (BGB-290) should be taken at approximately the same time, in the morning, for 7 days (up to 9 days if surgery is delayed) with the last preoperative dose taken 3 to 6 hours prior to surgery.

Accurately record the time that the dose is taken prior to the tumor resection. The surgical procedure must be performed at least 3 hours but not longer than 8 hours after dosing. The biopsy specimens submitted for drug concentration determinations should be resected as close to 3-6 hours after dosing as possible, but not more than 8 hours after dosing.

Collection, preparation and shipping instructions for the frozen tissue specimens and the corresponding blood samples are provided in the study lab manual.

10.0 OFF-TREATMENT/OFF-STUDY CRITERIA

Each subject has the right to withdraw from the study at any time without prejudice. The Investigator may discontinue any subject's participation for any reason, including AEs or failure to comply with the protocol (as judged by the Investigator, such as compliance below 80%, failure to maintain appointments, etc.).

Should a subject withdraw from the study, the reason(s) must be stated on the case report form and a final evaluation of the subject should be performed.

Patients who go off treatment must be followed for AEs for at least 30 days from the last dose of pamiparib (BGB-290).

10.1 Off-Treatment Criteria

1. Disease Progression: Remove patient from protocol therapy at the time progressive disease is documented. Disease progression is defined as: Progressive neurologic abnormalities not explained by causes unrelated to tumor progression (e.g. anticonvulsant or corticosteroid toxicity, electrolyte abnormalities, hyperglycemia, etc.) or a greater than 25% increase in the measurement of the tumor by MRI scan. If neurologic status deteriorates, on a stable or increasing dose of steroids, or if new lesions appear on serial MRI, further study treatment will be discontinued. Please refer to the Imaging Core Manual for further imaging requirements and submission information.

2. Adverse Event:
   - Intercurrent illness that prevents further administration of treatment
   - Patients who experience unacceptable toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

3. Patient Withdrawal: Patient's refusal to continue treatment: in this event, document the reason for withdrawal.

4. Non-Compliance: Failure to comply with protocol (as judged by the investigator such as compliance below 80%, failure to maintain appointments, etc.)

5. Physician Decision: If at any time the treating physician feels the constraints of this protocol are detrimental to the patient's health remove the patient from protocol therapy.

6. Protocol Defined Delay:
   - Patients will be off treatment who experience a treatment-related toxicity causing a delay in treatment >21 days. Note: Patients who experience grade 3 hepatic toxicity will be off treatment if treatment-is delayed >14 days.
   - Delay in protocol >28 days for major events or other non-treatment related delays
   - Patients who require >2 dose reductions

7. Death

10.2 Off-Study Criteria and Survival Follow-Up

Patients will only be off study at the time of death. Patients will be followed every two months for progression, for up to one year from the off-treatment date. All patients will be followed for survival every 2 months for the first 2 years from the off-treatment date; after 2 years, patients will be followed every 6 months until death. Survival status may be obtained by phone call, clinic visit, or medical records (e.g. physician notes/laboratory results of clinic or hospital visit).

11.0 STATISTICAL CONSIDERATIONS

Phase I /Dose Finding

The primary objective of the phase I study is to determine the safety combination treatment of pamiparib (BGB-290) given at a fixed dose level of 60 mg BID with TMZ 20 mg starting at the dose level/schedule 1 (Days 1-28), then subsequently dose level -1 (Days 1-21), dose level -2 (Days 1-14), and dose level -3 (Days 1-7) in patients with recurrent gliomas and IDH1/2 mutations. The standard 3+3 design will be used for dose finding. Three patients will be treated in a dose/schedule cohort and dose de-escalation/changing treatment schedule, if required will take a stepwise fashion with expansion to a total of 6 patients at a putative MTD/ or highest safe dose/schedule. The target DLT rate is 33%.

The MTD is defined as the combination regimen that yields a DLT rate less than, or equal to 33%.

The safety evaluation period is 28 days (the first cycle of treatment) for dose escalation decisions. All safety and toxicity will be followed and data will be collected till 90 days after discontinuation of the treatment.

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be used for scoring toxicity and adverse events. The severity and frequency of toxicity will be tabulated by the tested doses using descriptive statistics. The proportions of subjects who experienced grade 3 or above toxicities will be estimated, along with 95% confidence intervals by each type of toxicity.

The Phase II efficacy study will be warranted after a safe combination regimen is deemed.

Phase II/ Safety and Efficacy

The primary objective of the phase II portion of the study is to estimate treatment effect in terms of tumor radiographic response in two different patient populations independently. One is a poor risk patient population, alkylator resistant/alkylator-refractory: Arm A. The other is favorable risk patients who had one distant alkylator failure: Arm B.

Primary Endpoint:
The primary endpoint for both Arm A and B is tumor radiographic response (CR+PR) using Response Assessment in Neuro-Oncology (RANO) criteria by measurable disease.

Study Design /Sample Size:

Arm A: It is a single arm design to test a hypothesis of clinical benefit of 25% radiographic response rate (PR+CR) for patients who failed multiple prior alkylator therapies and are treated with BCB290+TMZ to compare a null of 5%. The sample size estimation is based on a 2-stage design (MiniMax). A total sample size of 25 patients yields 90% statistical power to detect 20% improvement from a null of 5% with a false positive rate at 5%. At the first stage, 15 patients will be enrolled onto the study. The trial will be stopped and the null hypothesis accepted if no response was obtained among the first 15 patients (0/15). Otherwise, the study will continue to stage 2. The probability of early stopping for futility is 0.46 when the null is true and 0.01 when a true response is 25%. Ten additional patients will be enrolled on the second stage of the trial. If 4 or more patients out of the 25 have objective response, the study will reject the null hypothesis to conclude that pamiparib (BGB-290) in combination with TMZ is effective to treat patients with recurrent, alkylator-refractory, and IDH1/2-mutant glioma.

Arm B: It is a single arm study to test a hypothesis of clinical benefit of 50% radiographic response rate (PR+CR) for patients who failed one prior alkylator therapy and are treated with BCB290+TMZ to compare a null of 30%. The sample size estimation is based on a 2-stage design (MiniMax). A total sample size of 53 patients yields 90% statistical power to detect a 20% improvement from a null of 30% with a false positive rate at 5%. At the first stage, 24 patients will be enrolled onto the study. The trial will be stopped and accept the null hypothesis if 7 or fewer responses were obtained among the first 24 patients ($\leq$ 7/24). Otherwise, the study will continue to stage 2. The probability of early stopping for futility is 0.57 when the null is true and 0.03 when a true response is 50%. Twenty-nine additional patients will be enrolled in the second stage of the trial. If 22 or more patients out of the 53 have objective responses, the study will reject the null hypothesis to conclude that pamiparib (BGB-290) in combination with TMZ is effective to treat patients with recurrent, IDH1/2-mutant glioma who failed initial alkylator therapy.

Additional considerations on first stage/interim analysis:
Pamiparib (BGB-290) is a potent and selective inhibitor of PARP1 and PARP2 showing potent DNA-trapping and anti-proliferative activity that may also interfere with DNA repair, delaying resistance of TMZ activity (IB). The possible mechanistic function of pamiparib (BGB-290) (a PARP inhibitor), might not result in tumor shrinkage directly but delay tumor growth when given in combination with TMZ. If the required number of tumor responses was not achieved at the first stage, at the same time if the tumor growth rate on FLAIR during 6 months of treatment is statistically significantly reduced compared to the growth rate 6 months prior to the treatment pre design below, *the findings will be presented and reviewed with CTEP to determine whether to proceed to the second stage of the trial.

This additional interim analysis of tumor growth rate on FLAIR will be exercised, if and only if the expected tumor response per standard RANO criteria was not observed after 6 months from the treatment.

The estimate of tumor growth rate on FLAIR is specifically used for slow growing tumor, especially for low-grade gliomas to seek a biological signal of activity of a study treatment (e.g. AG120-881-C-001, AG120-C-002, DFCI/HCC 14-045). The tumor growth rate on FLAIR of 6 months is defined as a percentage change in T2 hyperintense volume with a minimum of 3 scans at 2 months apart during a 6-month period.

Per patient, It will be considered a clinical meaningful treatment effect if there was a greater than or equal to a 50% reduction in the tumor growth rate on FLAIR of 6 months after treatment started compared to the growth rate of 6 months prior to the treatment.

Arm A (High risk patients): the study will consider that a 50% of patients with the tumor growth rate reduction >= 50% is clinical meaningful to compare with a null of 20%. A total of 15 patients in the interim analysis per primary design will have a statistical power of857% to detect 30% difference at a target significance level of 0.06 (1-sided). It requires 6 or more patients out of the 15 to achieve tumor growth rate reduction on FLAIR of 6-month >= 50%.

Arm B (Low risk patients): the study will consider that a 60% of patients with the tumor growth rate reduction >= 50% is clinical meaningful to compare with a null of 30%. A total of 24 patients in the interim analysis per primary design will have a statistical power of 89% to detect 30% difference at a target significance level of 0.05 (1-sided). It requires 12 or more patients out of the 24 to achieve tumor growth rate reduction on FLAIR of 6-month>= 50%.

The definition of response for the primary endpoint will follow the response criteria (section 8.0) with a confirmatory MRI scan at least 4 weeks apart from the initial scan of response. Probability of responses will be estimated using binomial distribution along with 95% confidence interval. Arm A and B will be evaluated independently.

Secondary Endpoints:

- Progression-free survival: the progression-free survival time is defined as the time from a date of treatment start to a date of the initial scan deemed tumor progression while patient is alive. The data will be censored if progressive disease was not observed at the time of data cut-off for analysis. Progression-free survival (PFS) and median PFS will be estimated using Kaplan-Meier method along with 95% confidence interval.

- Overall survival: survival time is defined as the time from a date of treatment started to a date of death. The data will be censored if patient was alive at the time of data cut-off for analysis. Overall survival (OS) and median OS will be estimated using Kaplan-Meier method along with 95% confidence interval.

- Duration of the response (CR or PR): the duration of response is defined as the time from a date of initial scan of a response to a date of the initial scan deemed tumor progression. Results of the duration will be summarized using descriptive statistics.

- Safety/toxicity: adverse events per CTCAE (version 5.0). The proportion of patients with serious or life threatening toxicities will be estimated along with 95% confidence intervals.

Exploratory Objectives:

1. To assess tumor response rates, PFS, and OS in patients with WHO grade IV glioblastoma (GBM) treated with pamiparib (BGB-290) and TMZ. Ten grade IV recurrent IDH1/2 mutant GBM patients will be enrolled on to the GBM Arm to be treated with pamiparib (BGB-290)+TMZ using the combination doses defined in the phase I portion. The sample size is not based on a statistical considerations but clinical feasibility. The same tumor response criteria, definitions of OS and PFS for Arm A and B also apply in this GBM Arm. A tumor response rate will be estimated using binomial distribution (exact method) along with 95% confidence interval. Duration of tumor response, PFS and OS will be summarized and presented using standard methods.

2. To assess the mutational landscape via whole-exome sequencing (WES) using the tumor tissue obtained from previous surgical resection or biopsy. Particular interests of mutated gene including ATRX, CIC, FUBP1 and CDK4. Overall description of possible mutations will be summarized descriptively using descriptive statistics. Possible association between mutations and treatment effect will be explored using statistical molding approach based on type of treatment outcomes. False discovery rate will be provided for any discovery results.

3. To assess gene expression patterns using RNA sequencing (RNAseq). Overall description of possible gene expression patterns using RNA sequencing will be summarized descriptively using descriptive statistics. Possible association

between change in gene expression level and treatment effect will be explored using a statistical modeling approach based on type of treatment outcomes and patterns of change in gene expression. False discovery rate will be provided for any discovery outcomes.

4. To assess the methylation profiling with Infinium Methylation Assays, methylation status will be quantified as either methylated or unmethylated. Methylation status will summarized using descriptive statistics. Possible association with treatment outcomes can be assessed using regression modeling.

5. To quantify 2-hydroxyglutarate (2HG) in archival FFPE specimens via LC-MS detection and correlate with treatment response. The tumor tissues also will be used to quantify cellular metabolism marker (2HG) through Liquid Chromatography-mass Spectrometry. 2HG concentration will be measured as pmol/mg tissue. Output data will be normalized prior to analysis and data will be summarized using descriptive statistics such as mean, standard deviation, and quantiles etc. Regression model could be used to explore possible association with treatment outcomes such as stable disease versus progressive disease (primary clinical outcome per RANO) at a specific landmark time, or treatment responders (tumor response per RANO) versus non-responders, or progression-free survival and survival time etc. False discovery rate will be provided for any discovery results.

6. To explore possible association of 2HG levels, somatic alterations, gene expression / methylation patterns in FFPE tumor tissue, person correlation coefficient or spearman correlation coefficient could be used according to characteristics of the data.

7. PK: to assess tumor tissue pamiparib (BGB-290) levels, 2HG, and PARylation in a patient subset treated with drug prior to re-resection. Ten clinically indicated surgical candidates will be enrolled onto the surgical arm for drug concentration and tissue biomarkers study. The concentration of pamiparib (BGB-290) will be determined in a 0.05-0.10 cm^3 (50-100 mg) section of tumor tissue obtained from a contrast enhancing and non-contrast enhancing region of the tumor. Data will be normalized (e.g. taking logarithms) prior to analysis. Concentration levels of pamiparib (BGB-290), 2HG, and PARylation will be summarized using descriptive statistics independently. To characterize the steady state pharmacokinetics at a given dose and sampling time. Individual subject plasma concentration-time curves will be analyzed by non-compartmental methods using routines supplied in the WinNonlin Professional Version 5.0 software package (Pharsight Corp., Cary, NC). The geometric mean ± standard deviation of the estimated values of the pharmacokinetic parameter for groups of subjects evaluated at the given dose level will be calculated. Pharmacokinetic parameters, such as $C_{max,}$ $C_{min,}$ and AUC etc will be summarized descriptively.

8. To evaluate changes in tumor growth rate of 6 months in subjects with non-enhancing glioma based on fluid attenuated inverse recovery (FLAIR) tumor volume measurements of serial MRI exams. The tumor growth rate of 6 months is defined as a percent change of FLAIR tumor volume with non-enhancing glioma during a 6-month period. The difference of tumor growth rate of 6 months prior to treatment and during/ after treatment will be analyzed using paired t-test.

9. To assess whether change in tumor growth rate (based on FLAIR tumor volume) in subjects with non-enhancing glioma before and after treatment is associated with progression by Response Assessment in Neuro-oncology for Low Grade Gliomas (RANO LGG; phase II patients only) or survival. Cox regression model will be used to assess such possible association adjusting for well-known clinical prognostic factors.

12.0 STUDY ADMINISTRATION

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.

12.1 Investigator's Study File

The Investigator's Study File must contain all essential documents as required by ICH E6, including IRB and governmental approvals with correspondence, informed consent forms, patient enrollment and identification logs, drug accountability records, staff *curriculum vitae*, authorization forms and other appropriate documents/correspondence etc.

12.2 Source Data/Documents

Patient source documents used to record key efficacy/safety parameters, independent of the CRFs, may include for example, patient hospital/clinic records, original laboratory reports, ECG read-outs, MRI reports, pathology and special assessment reports, etc.

Source documents are part of the study documents and must be maintained, and direct access to source documents made available upon request, for monitoring visits, IRB review, audits or inspections. All source documents used to verify answers on CRFs will be uploaded to RAVE, including all documentation to prove eligibility criteria was meet.

12.3 Document Retention and Archiving

The Investigator must keep all study documents on file for at least 5 years after completion or discontinuation of the study. Subsequently, the Sponsor will inform the Investigator when the study documents can be destroyed, subject to local regulations.

These files must be made available for inspection, upon reasonable request, to authorized representatives of Sponsor or regulatory authorities.

Should the Investigator wish to assign the study records to another party, or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee the archiving requirement at the investigational site for any or all of the documents, arrangements must be made between the Investigator and the Sponsor for appropriate storage.

12.4 Data Collection/Reporting

Data collection for this study will be done exclusively through CTEP's Medidata Rave.

Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. In addition, site users that are a member of the ABTC must have the Rave CRA role in RSS at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive an invitation from iMedidata to activate their account. If you have any questions please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

- All data are due within 14 days of evaluation time point. Please see Section 9.1 for evaluation time points. Note: Source documentation to verify each CRF must be uploaded into Rave.
- Serious Adverse Events, PHONE IMMEDIATELY, SEE SECTION 9.3

This study will be monitored by the Clinical Data Update System (CDUS) Abbreviated Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. The ABTC Central Office is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.5 Study Monitoring

The ABTC Study Monitor (Sponsor) will remotely monitor the Investigator and study team on a regular basis throughout the study to verify the adherence to Good Clinical Practice (GCP), the protocol and the completeness, consistency and accuracy of the data being entered into the CRFs. The Study Monitor will also ensure that the study drug is being stored, dispensed, and accounted for according to specifications.

The Study Monitor will only conduct target on-site monitoring (See ABTC Monitoring plan for details). If on sight monitoring is necessary, the Investigator shall ensure that the study monitor has direct access to all required study data (source documents) during the visits. This includes all patient records needed to verify the entries in the CRFs, regulatory documents, pharmacy records or any other documents of concern.

The Investigator agrees to cooperate with the Study Monitor and ABTC to ensure that any deviations or issues detected in the course of monitoring visits are resolved.

12.6 Audits and Inspections

The study may be audited at any time, with appropriate notification, by qualified personnel from the Sponsor or its designees, to assess compliance with the protocol, GCP and regulatory requirements. These audits may also be conducted for quality assurance to ensure that complete and accurate data are submitted and that adverse events, complications and/or adverse reactions are being identified and reported.

The study may also be inspected by health authority inspectors, after appropriate notification. In the event of an audit or an inspection, the Investigator must ensure that direct access to all study documentation, including source documents, is granted to the auditors or inspectors.

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14.0 ETHICAL AND LEGAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki and in compliance with all applicable laws and regulations of the locale where the study is conducted.

It is the responsibility of the Investigator that the patient is made aware and consent is given that personal information may be scrutinized during audits by competent authorities and properly authorized persons, but that personal information will be treated as strictly confidential and not be publicly available. The Investigator is responsible for the retention of the patient log and patient records.

APPENDIX I – PATIENT MEDICATION DIARIES

Pamiparib (BGB-290) DIARY (Pamiparib (BGB-290) twice every day in 28-day cycles): **Phase I patients; Phase II patients; Surgical Portion patients in post-surgical cycles**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take pamiparib (BGB-290) _____ mg (___ capsules) twice per day. Take doses about 12 hours apart at approximately the same times each day.
2. You must fast for at least 1 hour before and 2 hours after taking the study drug. Water is allowed during the fasting period.
3. Take pamiparib (BGB-290) with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush.
4. Record the date and the time you took each pamiparib (BGB-290) dose.
5. Record missed or skipped dose(s). If you miss a dose you may make up that dose if you take it within 2 hours of the time you normally take it. There must be at least 8 hours before the next dose.
6. If you vomit a dose, do not re-take the study drug. Take the next dose at the time that you normally take the next scheduled dose.
7. Bring this form and any remaining pamiparib (BGB-290) capsules when you come in for you clinic visits.

Week	Day	Date	Time of dose morning dose	# of capsules	Time of dose evening dose	# of capsules	Comments
1	1						
	2						
	3						
	4						
	5						
	6						
	7						
2	8						
	9						
	10						
	11						
	12						
	13						
	14						
3	15						
	16						
	17						
	18						
	19						
	20						
	21						
4	22						
	23						
	24						
	25						
	26						
	27						
	28						

Patient's Signature _____ **Date**_____

Nurse's Signature _____ **Date** _____

Pamiparib (BGB-290) DIARY (Pamiparib (BGB-290) daily for 7-9 days before surgery)**: Surgical Portion patients–Pre-Surgical Treatment**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. You will take pamiparib (BGB-290) _____ mg (___ capsules) twice per day staring 6 days prior to your scheduled surgery. Take doses about 12 hours apart at approximately the same times each day.
2. You must fast for at least 1 hour before and 2 hours after taking the study drug. Water is allowed during the fasting period.
3. Take pamiparib (BGB-290) with 8 ounces of water. Capsules should be swallowed whole, do not chew or crush.
4. Record the date and the time you took each pamiparib (BGB-290) dose.
5. Record missed or skipped dose(s). If you miss a dose you may make up that dose if you take it within 2 hours of the time you normally take it. There must be at least 8 hours before the next dose.
6. If you vomit a dose, do not re-take the study drug. Take the next dose at the time that you normally take the next scheduled dose.
7. Bring this form and any remaining pamiparib (BGB-290) capsules when you come in for your surgery

Day	Dose of Pamiparib (BGB-290)	Date	Time of morning dose	# of capsules	Time of evening dose	# of capsules	Comments
Day 1: 6 days prior to surgery							
Day 2: 5 days prior to surgery							
Day 3: 4 days prior to surgery							
Day 4: 3 days prior to surgery							
Day 5: 2 days prior to surgery							
Day 6: 1 day prior to surgery							
(additional day if surgery is delayed)							
(additional day if surgery is delayed)							
Day of surgical resection, 3-6 hrs. before surgery							

Patient's Signature _____ **Date**_____

Nurse's Signature _____ **Date** _____

TEMOZOLOMIDE DIARY Temozolomide daily on Days 1-28 of every 28-day cycle)

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **20 mg of Temozolomide (TMZ) on Days 1-28 of every 28-day cycle**.
   Take the capsule on an empty stomach, 1 hour before a meal or 1 hour after, with water approximately the same times each day.
2. On the days that the two drugs are given together, TMZ should be taken at the same time as the morning dose of pamiparib (BGB-290).
3. If you miss a dose, you can take it within 6 hours after you normally take it.
4. If you vomit after taking your TMZ, you should not retake that dose, resume taking your TMZ at the next scheduled dose.
   Dose: one 20 mg capsule. Record the date, the time you took the 20 mg capsule.
   Record missed or skipped dose(s).
5. Bring this form and your bottles of TMZ capsules when you return for each appointment.

Week	Day	Date	Time of dose	Comments
1	1			
	2			
	3			
	4			
	5			
	6			
	7			
2	8			
	9			
	10			
	11			
	12			
	13			
	14			
3	15			
	16			
	17			
	18			
	19			
	20			
	21			
4	22			
	23			
	24			
	25			
	26			
	27			
	28			

Patient's Signature _____ **Date**_____

Nurse's Signature _____ **Date** _____

TEMOZOLOMIDE DIARY Temozolomide daily on Days 1-21 of every 28-day cycle)

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **20 mg of Temozolomide (TMZ) on Days 1-21 of every 28-day cycle**.
   Take the capsule on an empty stomach, 1 hour before a meal or 1 hour after with water approximately the same times each day.
2. Except for on the days that the two drugs are given together, TMZ should be taken at the same time as the morning dose of pamiparib (BGB-290).
3. If you miss a dose, you can take it within 6 hours after you normally take it.
4. If you vomit after taking your TMZ, you should not retake that dose, resume taking your TMZ at the next scheduled dose.

Dose: one 20 mg capsule. Record the date, the time you took the 20 mg capsule.
Record missed or skipped dose(s).

1. Bring this form and your bottles of TMZ capsules when you return for each appointment.

Week	Day	Date	Time of dose	Comments
1	1			
	2			
	3			
	4			
	5			
	6			
	7			
2	8			
	9			
	10			
	11			
	12			
	13			
	14			
3	15			
	16			
	17			
	18			
	19			
	20			
	21			
4	22	(no dose)	–	
	23	(no dose)	–	
	24	(no dose)	–	
	25	(no dose)	–	
	26	(no dose)	–	
	27	(no dose)	–	
	28	(no dose)	–	

Patient's Signature _____ **Date**_____
Nurse's Signature _____ **Date** _____

TEMOZOLOMIDE DIARY Temozolomide daily on Days 1-14 of every 28-day cycle)

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **20 mg of Temozolomide (TMZ) on Days 1-14 of every 28-day cycle**.
   Take the capsule on an empty stomach, 1 hour before a meal or 1 hour after with water approximately the same times each day
2. Except for on the days that the two drugs are given together, TMZ should be taken at the same time as the morning dose of pamiparib (BGB-290)
3. If you miss a dose, you can take it within 6 hours after you normally take it.
4. If you vomit after taking your TMZ, you should not retake that dose, resume taking your TMZ at the next scheduled dose
   Dose: one 20 mg capsule. Record the date, the time you took the 20 mg capsule.
   Record missed or skipped dose(s).
5. Bring this form and your bottles of TMZ capsules when you return for each appointment.

Week	Day	Date	Time of dose	Comments
1	1			
	2			
	3			
	4			
	5			
	6			
	7			
2	8			
	9			
	10			
	11			
	12			
	13			
	14			
3	15	(no dose)	–	
	16	(no dose)	–	
	17	(no dose)	–	
	18	(no dose)	–	
	19	(no dose)	–	
	20	(no dose)	–	
	21	(no dose)	–	
4	22	(no dose)	–	
	23	(no dose)	–	
	24	(no dose)	–	
	25	(no dose)	–	
	26	(no dose)	–	
	27	(no dose)	–	
	28	(no dose)	–	

Patient's Signature _____ **Date**_____

Nurse's Signature _____ **Date** _____

TEMOZOLOMIDE DIARY Temozolomide daily on Days 1-7 of every 28-day cycle)

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

Cycle # _____

INSTRUCTIONS TO THE PATIENT:

1. You will take **20 mg of Temozolomide (TMZ) on Days 1-7 of every 28-day cycle**.
   Take the capsule on an empty stomach, 1 hour before a meal or 1 hour after, with water approximately the same times each day.
2. Except for on the days that the two drugs are given together, TMZ should be taken at the same time as the morning dose of pamiparib (BGB-290).
3. If you miss a dose, you can take it within 6 hours after you normally take it.
4. If you vomit after taking your TMZ, you should not retake that dose, resume taking your TMZ at the next scheduled dose.
   Dose: one 20 mg capsule. Record the date, the time you took the 20 mg capsule.
   Record missed or skipped dose(s).
5. Bring this form and your bottles of TMZ capsules when you return for each appointment.

Week	Day	Date	Time of dose	Comments
1	1			
	2			
	3			
	4			
	5			
	6			
	7			
2	8	(no dose)	–	
	9	(no dose)	–	
	10	(no dose)	–	
	11	(no dose)	–	
	12	(no dose)	–	
	13	(no dose)	–	
	14	(no dose)	–	
3	15	(no dose)	–	
	16	(no dose)	–	
	17	(no dose)	–	
	18	(no dose)	–	
	19	(no dose)	–	
	20	(no dose)	–	
	21	(no dose)	–	
4	22	(no dose)	–	
	23	(no dose)	–	
	24	(no dose)	–	
	25	(no dose)	–	
	26	(no dose)	–	
	27	(no dose)	–	
	28	(no dose)	–	

Patient's Signature _____ **Date**_____

Nurse's Signature _____ **Date** _____

APPENDIX II – PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, ***pamiparib (BGB-290)***. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Pamiparib (BGB-290) interacts with certain specific enzymes in your liver*.

> *The enzymes in question are **CYP3A, CYP2C9, and CYP2C8,** and pamiparib (BGB-290) is broken down by these enzymes and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Pamiparib (BGB-290) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Pamiparib (BGB-290) must be used very carefully with other medicines that use certain **liver enzymes to be effective or to be cleared from your system**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/strong and moderate inhibitors or substrates of **CYP3A**: these medicines or supplements are prohibited while taking pamiparib (BGB-290). Medicines and herbal supplements that are considered **CYP2C9** substrates or strong **CYP2C8** inhibitors should be used with caution.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or

pharmacist to determine if there could be any side effects.

- See the list below of medicines that are either prohibited on this trial or should only be used with caution
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

Prohibited Medications

Strong CYP3A Inducers:
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, firabutin, rifampin (rifampicin), St. John's wort (hypericumperforatum)

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

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

Medications to be used with caution:

Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index:
Celecoxib
Phenytoin
Warfarin

Strong CYP2C8 Inhibitors
Gemfibrozil

STUDY DRUG INFORMATION WALLET CARD	**Pamiparib (BGB-290)** interacts with **specific liver enzymes called CYP3A, CYP2C9, and CYP2C8**, and must be used very carefully with other medicines that interact with these enzymes.
You are enrolled on a clinical trial using the experimental study drug **Pamiparib** (**BGB-290).** This clinical trial is sponsored by the NCI. _____ may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A, CYP2C9, and CYP2C8. ➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____.

APPENDIX III – CONTRACEPTION & PREGNANCY

Women of childbearing potential must have a negative serum pregnancy test within 7 days of randomization. Women of childbearing potential and men must agree to use highly effective contraception (preferably those with low user dependency) prior to study entry, for the duration of study participation, and for at least 6 months after the last dose of study drug.

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control.

Highly effective contraception includes:

- Combined (estrogen- and progestogen-containing) hormonal contraception (oral [also called "birth control pills"], intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with the inhibition of ovulation (oral, injectable, or implantable*)
- Intrauterine device (also called IUD)*
- Intrauterine hormone-releasing system (also called IUS)*
- Bilateral tubal occlusion (tying the tubes)*
- Vasectomized male partner*, provided that the vasectomized partner is the only sexual partner of the woman of childbearing potential. Vasectomy is a surgical procedure to cut and seal the tube used to transport semen from the testicles to the penis.
- Sexual abstinence (defined as refraining from having sex with a person from the opposite sex) during the entire period of exposure associated with the study treatment.

NOTE: Total sexual abstinence should be used as a contraceptive method only if it is in line with the participant's usual and preferred lifestyle. Periodic abstinence (for example, calendar, ovulation, natural family planning methods), declaration of abstinence for the duration of exposure to study treatment, and withdrawal (ejaculation outside of the sexual partner's body) are not acceptable methods of contraception.

*Contraception methods that in the context of this protocol are considered to have low user dependency.

Patients should consult their physician regarding what contraceptive method should be used. It should be noted, however, that barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of birth control or pregnancy prevention and if used must be combined with a highly effective contraceptive method.

Women of childbearing potential must also agree to monthly pregnancy tests through 6 months after completion of pamiparib (BGB-290) or temozolomide administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study or within 6 months after completing the study treatment, she should inform her treating physician immediately. The study doctor will monitor the pregnancy at least up to completion and at most up to 8 weeks following the delivery date (refer to Monitoring Pregnancy Section for more details). In addition, women who become pregnant while participating in the study must immediately stop

taking study treatment. Men treated or enrolled on this protocol must also agree to use condoms in addition to 1 of the highly effective methods of contraception (listed above) prior to the study, for the duration of study participation, and through 6 months after completion of pamiparib (BGB-290) or temozolomide administration. If a female partner of a male patient is already pregnant, the male patient must use condoms during sexual intercourse for the duration of the study and for at least 6 months after the last dose of pamiparib (BGB-290).
Women and men should not donate and/or freeze egg/sperm while participating in the study and for at least 6 months after completing study treatment.

If a woman or man is in an exclusive same-sex relationship and is not engaged in attempts to become pregnant or father a child, it is not necessary to use a highly effective contraceptive method.

Definitions of "Women of Childbearing Potential", "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are females who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as females meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, 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 postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15,2014
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-CTFG/2014_09_HMA_CTFG_Contraception.pdf