ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A071102

A PHASE II/III RANDOMIZED TRIAL OF VELIPARIB OR PLACEBO IN COMBINATION WITH ADJUVANT TEMOZOLOMIDE IN NEWLY DIAGNOSED GLIOBLASTOMA WITH MGMT PROMOTER HYPERMETHYLATION

Investigational Agent: veliparib (NSC #737664, IND # 122646) will be supplied by NCI DCTD- CTEP IND
Commercial agent(s): temozolomide
Imaging site credentialing required for participation
ClinicalTrials.gov Identifier: NCT02152982

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Closure
[X]	Informed Consent changes	[ ]	Suspension / temporary closure
[ ]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[ ]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[ ]	Other :		

IRB review and approval of this update is required within 90 days. Expedited review is allowed. Please follow your local IRB guidelines.

UPDATES TO THE PROTOCOL:

References to the "Alliance Imaging Core lab (ICL),", "ICL," and the email address "Alliance071101@ImagingCoreLab.com" have been changed to "Imaging and Radiation Oncology Core (IROC),", "IROC," and "Alliance071102@irocohio.org," respectively throughout ought the protocol document.

Cover Page

- "CTEP IND" has been added beneath the title to reflect the name of the IND holder.
- The text "NCT" from the "Clinical Trials Identifier" listed at the top of the page was duplicated and has been deleted. It now reads, "NCT02152982."
- The following statement has been added at the top of the page: "Imaging credentialing required for participation."
- At the bottom of the second page, in the "Document History" table, "Pre-activation" has been changed to "Activation" and the word "Date" has been removed from the row beneath "Effective

Date." The protocol activation date has been added.

Schema

- Beneath the "Required Initial Laboratory Values" for "AST and ALT", "≤ 3 x normal range" has been changed to "≤ 3 x ULN."
- At the bottom, of the page, "Treatment is to continue for up to 6 months or until disease progression or unacceptable adverse event. Patients will be followed for progression or death for five years. After 5 years patients are followed for survival only" has been changed to "Treatment is to continue for up to 6 months or until disease progression (confirmed progression) or unacceptable adverse event. Patients will be followed for progression for up to 5 years. Patients will be followed for survival for up to 10 years.

Section 1.0 Background

- The rationale for the six months of temozolomide has been added at the bottom of this section.

Section 3.3.3 Required Lab Values

- The footnote superscript "2" has been removed from the laboratory values for creatinine as it was a typographical error.
- The "Required Initial Laboratory Values" for "AST and ALT", have been changed from "≤ 3 x normal range" to "≤ 3 x ULN."

Section 5.0 Study Calendar

- Reference to the newly added footnote "***" has been added to the timepoint "Baseline (Before start of treatment)" beneath the row title "Correlative studies: For patients who consent to participate." Below the table, this footnote reads," "It is strongly preferred that the research blood sample is drawn prior to start of study therapy, however, it is acceptable to submit within 60 days of registration to the treatment trial."
- The word "confirmed" has been added to the third sentence in footnote 8. It now reads, "For patients who have progressive disease, submit one scan after confirmed progression and no further scans."
- In footnote 9, the phrase, "…both prior to radiation and…" has been added. It now reads, "Must be done both prior to radiation and 21-42 days after completion of radiation and temozolomide."
- Footnote 11 has been changed from "Physical exams and MR are required every 3 months (+/- 14 days) for the first 3 years, then every 6 months (+/- 28 days) in years 4 and 5, or until unequivocal progression; thereafter, survival calls only are required" to "Physical exams and MR are required every 3 months (+/- 14 days) for the first 3 years, then every 6 months (+/- 28 days) in years 4 and 5, or until confirmed progression, after which one additional MR is to be submitted; thereafter, survival calls every 6 months only are required. See Section 11.4.3.1."

Section 6.2 Pathology Considerations: Tissue Specimen Collection and Submission

- References to the following footnotes "*,***" have been added to the tissue block requirement beneath the column header title "For patients registered to A071102-ST1, submit the following: Optional."
- The following "Note" has been added to footnote 3 for clarity: "It is strongly encouraged that whole blood samples are collected prior to the initiation of study treatment. However, sample collection and registration to the –ST2 sub-study may take place within 60 days of registration to the treatment trial."

Section 6.5 CT and MRI Imaging Data Submission

- The word "confirmed" has been added to the third sentence of the first paragraph. It now reads, "For patients who have progressive disease, submit one scan after confirmed progression and no further scans."
- Beneath "Submit these data to", the reference to "A091105" has been changed to "A071102," as this was included in error.

Section 7.0 Treatment Plan/Intervention

- The parenthetical reference "(confirmed progression)" has been added to the fourth paragraph. It now reads; "Protocol therapy will consist of 6 cycles administered on days 1-7 of each 28 day cycle. Treatment will continue until disease progression (confirmed progression) or unacceptable adverse event or maximizing the dose reductions, for a maximum period of 6 cycles.

Section 9.0 Adverse Events

- The second paragraph has been revised in its entirety as the process for event reporting has been modified. The former third paragraph has been removed as a result.

Section 9.3 CTEP Adverse Event Reporting System (CTEP-AERS)

- The first paragraph has been added for clarity.
- In the second paragraph, the third and fourth sentences have been changed from "All such must be reported in an expedited manner using CTEP Adverse Event Reporting System (CTEP-AERS). Expedited AE reporting for this study must only use CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP home page, http://ctep.cancer.gov" to "All expedited reports will occur through the CTEP Adverse Event Reporting System (CTEP-AERS). This system can be accessed via the CTEP home page, http://ctep.cancer.gov."

Section 11.1 Schedule of Evaluations

- In this section, the word "unequivocal" has been replaced with the word "confirmed." It now reads, "For the purposes of this study, patients should be reevaluated every 8 weeks while on therapy and then at a minimum every 3 months for years 1-3 and every 6 months for years 4 and 5 after completion of therapy, or until confirmed progression."

Section 11.4.3.1 Response Criteria

- The word "confirmed" has been added to the second sentence of the second paragraph. It now reads, "If subsequent imaging studies and/or clinical observations demonstrate that progression in fact has occurred, the date of confirmed progression should be noted as the scan at which the potential progression was first identified."

Section 11.4.4 Overall Objective Status

- The following "Note" has been added for clarity underneath the first paragraph: "Patients with possible PsP should initially be given the Objective Status of Preliminary Progression. Once PsP or Progression is confirmed, the Objective Status can be changed accordingly."
- In the table, under the "Overall Objective Status" column, the word "confirmed" has been added in front of "PD" for "PD" and "CR/PR/SD/PD/Not all Evaluated."
- In the table, under the "Target Lesions" and "Overall Objective Status" columns, "Possible PsP" and "Preliminary PD" have been added respectively.

Section 12.1.1 CR, PR or SD

- The parenthetical reference "(preliminary progression)" has been added to the second sentence. It now reads, "Patients with possible pseudoprogression (preliminiary progression) also should remain on therapy."

Section 15.1 Institutional credentialing

- In the first paragraph, the word "enrollment" has been changed to "pre-registration." It now reads, "Prior to the pre-registration of the first patient, the Imaging and Radiation Oncology Core (IROC) must approve institutions to participate in the A071102 imaging study."

Appendix II: Standard MRI Protocols

- This section has been updated in its entirety to reflect the current standard and advanced imaging protocols.

CHANGES TO THE SCREENING CONSENT

Signature

- Beneath the participant's date of signature, the parenthetical reference, "(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor)" has been deleted.

CHANGES TO THE TREATMENT CONSENT

What are the study groups?

- Although the group labels "Group 1" and "Group 2" had no bearing on the treatment assignment, in the paragraphs that describe the two study groups, "Group 1" has been changed to "One group" and "Group 2" has been changed to "The other group." It now reads, "One group will get the usual chemotherapy drug (temozolomide) used for this type of cancer plus a placebo pill (a sugar pill that looks like veliparib) and "The other group will get the usual chemotherapy drug (temozolomide) used for this type of cancer plus a study drug called veliparib" respectively.
- The headings "Group 1" and "Group 2" have been removed from the schema, and "Chemotherapy" has been replaced with "TMZ" for clarity.
- Under "The other group" the word "placebo" has been removed from the third bullet. It now reads, "Veliparib should be taken twice a day (approximately 12 hours apart), without regard to meals."

How long will I be in this study?

- In the first and second sentences, "TMZ and veliparib/placebo" has been changed to "TMZ/placebo or TMZ/veliparib" for clarity.

What are the costs of taking part in this study?

- "Veliparib/placebo" has been changed to "Veliparib or placebo

Signature

- To be consistent with the NCI's consent form template, a space that allows for the signature and date of the person(s) conducting the informed consent discussion and date has been added to the bottom of the treatment consent.

A replacement protocol document and model consent have been issued

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ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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ClinicalTrials.gov Identifier: NCT02152982

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Study Resources:

CTEPAdverse Event Reporting System
https://eapps-ctep.nci.nih.gov/ctepaers/

Medidata Rave® iMedidata portal
https://login.imedidata.com

OPEN (Oncology Patient Enrollment Network)
https://open.ctsu.org

Biospecimen Management System
http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review:	Regulatory Affairs Manager: *regulatory@alliancenctn.org*
Questions regarding CTEP-AERS reporting:	Regulatory Affairs Manager: *regulatory@alliancenctn.org* or (773) 702-9814
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Mayo Clinic

Document History	Effective Date:
Activation	12/15/2014
Update #01	04/15/2015

CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network OPEN which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	*All participating sites will submit study data via Medidata Rave System.* Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

For clinical questions (i.e., patient eligibility or treatment-related) see the Protocol Contacts, Page 2.

For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org> education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy

The CTSU Web site is located at https://www.ctsu.org.

Randomized trial of veliparib or placebo in combination with adjuvant temozolomide in newly diagnosed GBM with MGMT promoter hypermethylation

Patient Eligibility for Pre-Registration
Newly diagnosed Grade IV intracranial glioblastoma or gliosarcoma
Sufficient tissue available for central pathology review and MGMT methylation status evaluation
Age ≥ 18 years

Patient Eligibility for Registration
Tumor MGMT promoter hypermethylation
Confirmation by central pathology review of WHO Grade IV glioblastoma or gliosarcoma
Completion of concomitant radiation and TMZ with adequate recovery from toxicity
Radiation dose and schedule conform to minimum standard defined in Appendix I.
TMZ dosing schedule during radiation conforms to minimum standard defined in Appendix I.
ECOG performance status of ≤ 2
Non-pregnant/non-nursing
Patients must sign an informed consent prior to analysis of MGMT promoter methylation and a second study-specific informed consent prior to study registration.

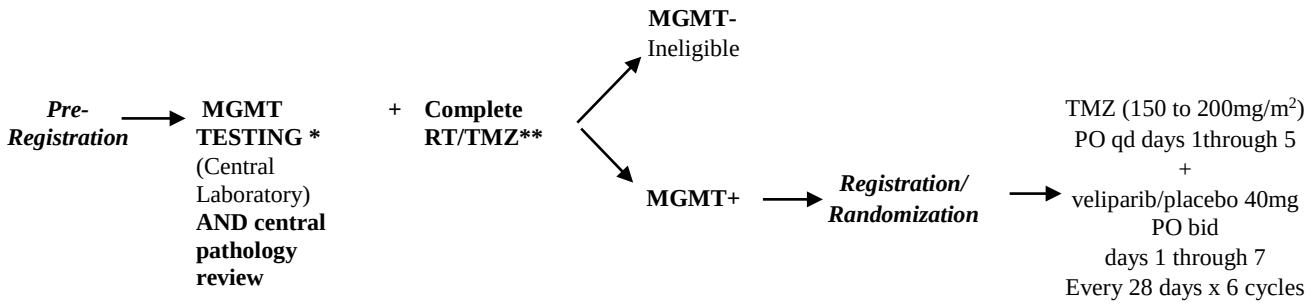
Required Initial Laboratory Values
(Within 14 days prior to study registration)

Absolute neutrophil count (ANC)	≥ 1500 cells/mm^3
Platelets	≥ 100,000 cells/mm^3
Creatinine	≤ 1.5x ULN
Bilirubin [1]	≤ 1.5x ULN
AST and ALT	≤ 3 x ULN

[1] Unless patient has Gilbert's disease

Schema

1 Cycle = 28 Days



*MGMT testing can be done at any time as long as the patient is randomized to treatment within 28-42 days after RT/TMZ completion.

**Must monitor CBC during RT + TMZ.

Treatment is to continue for up to 6 months or until disease progression (confirmed progression) or unacceptable adverse event. Patients will be followed for progression for up to 5 years. Patients will be followed for survival for up to 10 years.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

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1.0 Background

Glioblastoma multiforme (GBM) is the most common primary adult brain tumor and is uniformly fatal. Recent studies have demonstrated a significant survival benefit for combining temozolomide (TMZ) chemotherapy with standard radiation therapy following optimal surgical debulking (1). Response to TMZ therapy is significantly influenced by promoter methylation of the DNA repair gene O6-methylguanine-methyltransferase (MGMT). For patients enrolled on the EORTC 22981 trial and treated with radiation and TMZ, tumor MGMT promoter hypermethylation was associated with a 46% 2 year survival, while lack of promoter methylation was associated with a 14% 2 year survival (2). The extent of survival benefit with TMZ-based therapy in patients with MGMT-methylated tumors is unparalleled by any other novel therapeutic in current clinical or pre-clinical studies, and this observation supports the general rationale for pursuing novel TMZ-sensitizing strategies in an attempt to obtain further survival gains with this efficacious therapy. Aside from FDA approval of temozolomide, there has been little progress in developing more efficacious therapies for newly diagnosed GBM. Bevacizumab has shown promise in recurrent GBM, but two clinical trials of bevacizumab combined with conventional radiation and temozolomide failed to demonstrate a survival benefit for the combination compared to treatment with radiation and temozolomide alone. Thus, there is an urgent need to develop novel therapies for GBM patients.

This clinical trial will evaluate the combination of a PARP inhibitor with adjuvant temozolomide after completion of concurrent radiation and temozolomide therapy. Based on extensive pre-clinical animal studies detailed below, we have made several observations that critically inform the design of this clinical trial. First, veliparib combined with TMZ alone can markedly enhance the efficacy of therapy. Second, the combination of veliparib with TMZ is ineffective in tumors with acquired TMZ resistance. Third, the combination of veliparib with TMZ is ineffective in TMZ-naïve GBM tumors that are inherently resistant to TMZ. Fourth, lack of MGMT expression is critical for the sensitizing effects of veliparib combined with TMZ. From these data, **we hypothesize** that tumor MGMT promoter hypermethylation can be used as an integral biomarker and key entry criteria for this randomized Phase II/III clinical trial to enrich for patients most likely to benefit from the combination of veliparib with adjuvant TMZ compared to adjuvant TMZ alone following completion of concurrent radiation/temozolomide therapy. Although the prognosis for MGMT hypermethylated tumors is better than for unmethylated tumors, the 5-year survival for MGMT promoter hypermethylated tumors is less than 5%. Thus, if successful, this clinical trial could significantly improve survival for this subset of patients.

The rationale for the six months of temozolomide is the following;

- The FDA label is for 6 cycles of TMZ
- The RTOG0525 study indirectly addresses the question of the extent of benefit for greater TMZ exposure. In this trial, the patients receiving dose-dense TMZ (50% greater TMZ exposure) did not have a survival advantage. At a gross level, this suggests that more TMZ is not necessarily better.
- The combination of veliparib and TMZ may be associated with higher toxicities, so extended dosing with the combination may not be as well tolerated as TMZ alone.

1.1 Rationale for selected approach and trial design

Repair of TMZ-induced DNA methylation lesions

TMZ leads to methylation of nucleotide bases in genomic DNA, and disruption of replication by un-repaired methylation damage is responsible for inducing cell death. The common methylation lesions N7-methylguanine and N3-methyladenine are efficiently repaired by base-

excision repair (BER). In contrast, the highly mutagenic and cytotoxic lesion O6-methylguanine (O6MG) is repaired in a one-step process by MGMT. Both BER and MGMT are critical for cell survival, and either BER or MGMT repair inhibitors significantly enhance TMZ cytotoxicity (3-11). PARP1/2 functions as a scaffold for other BER-proteins, and disruption of BER function by PARP inhibition has been widely viewed as a key mechanism accounting for the TMZ-sensitizing effects of PARP inhibitors (reviewed in (12)). However, at least one study demonstrated that the TMZ sensitizing effects of a PARP inhibitor are seen at inhibitor concentrations 10-fold lower than those associated with disruption of BER (13). Moreover, we have extensive *in vivo* preliminary data demonstrating that the PARP inhibitor veliparib preferentially sensitizes tumors that are inherently sensitive to TMZ. Since effective BER inhibition should increase TMZ sensitivity in essentially all tumors (14-16), our preliminary data suggest that PARP inhibitors may not sufficiently suppress BER when used in a clinically relevant dosing schedule in our highly clinically relevant orthotopic xenograft therapy evaluation model.

Role of homologous recombination (HR) in tolerance of O6MG DNA lesions

O6MG is the key cytotoxic lesion induced by TMZ, and we hypothesize that PARP inhibitor efficacy is linked to repair processing of this lesion. Persistent O6MG is mispaired with thymidine during replication and subsequently engaged by futile cycles of mismatch repair (MMR) that ultimately result in collapsed replication forks. Recovery from stalled replication requires HR-mediated DNA repair (17, 18). Core HR activity is modulated by Rad51 and 5 paralogs (XRCC2, XRCC3, RAD51B, RAD51C and RAD51D), and disruption of any one of these family members results in chromosomal instability, hypersensitivity to crosslinking agents, defective RAD51 foci formation, and decreased HR activities (19-22). Consistent with the likely exclusive role for HR in mediating recovery following replication fork collapse, multiple models have demonstrated significant sensitivity of HR-defective cells to replication inhibitors (23, 24). Others have shown that HR-defective cells are hypersensitive to alkylating agents (25, 26). In one study, cells with combined defects in MGMT and HR (either XRCC2 or BRCA2 mutation) were highly sensitive to TMZ, and restoration of MGMT expression almost completely abolished the hypersensitivity observed in the HR-defective cells (27). These latter data demonstrate that the replication-arresting O6MG lesions induced by TMZ are specifically processed by HR and that deregulation of HR can have a significant impact on treatment efficacy.

Poly(ADP-ribose) polymerase functionality in DNA repair

PARP-1 and PARP-2 play key roles in the modulation of DNA repair. The proteins catalyze the poly-ADP-ribosylation of target proteins to form a branched nucleic acid-like polymer poly-ADP-ribose (PAR). PAR modifications modulate protein functions and are dynamically regulated (reviewed in 12). At sites of DNA damage, PARP ribosylates itself and multiple target proteins and modulates activity of other proteins through direct interactions. Disruption of PARP activity leads to significant chemosensitizing effects in combination with alkylating agents, topoisomerase inhibitors, and DNA cross-linking agents (28-30). Thus, there is strong clinical interest in understanding how PARP inhibitors modulate recovery from DNA damage.

PARP plays a key function in modulating HR, and this functionality is likely a key contributor to the clinical efficacy of PARP inhibitors. While PARP does not directly interact with Rad51, PARP inhibition results in a hyper-recombinogenic phenotype associated with elevated sister-chromatid exchanges (SCE) and increased Rad51 foci formation (31, 32). PARP deficient cells are hypersensitive to hydroxyurea (HU)-induced replication arrest, and recovery following HU treatment in these cells is associated with elevated levels of sister chromatid exchanges, increased Rad51 foci formation and delayed exit from S-phase (33). Consistent with these data, PARP inhibition can delay the initiation of HR-mediated repair of stalled replication forks (33). While the detailed mechanistic interactions of PARP with HR are not fully understood, several

pre-clinical and clinical studies have demonstrated that tumors defective in HR are hypersensitive to PARP inhibitors, either alone or in combination with cytotoxic chemotherapies (34-39). Specifically relevant to this application, a recent study presented in 2010 at ASCO of veliparib combined with TMZ in metastatic breast cancer patients demonstrated efficacy only in the subset of patients harboring BRCA1 or 2 mutations (40). These data highlight the potential importance of HR integrity on the efficacy of PARP inhibitor combinations, and in some of the correlative studies proposed, we will evaluate whether molecular deficiencies within the HR pathway affect the TMZ-sensitizing effects of PARP inhibition in patient samples collected on this trial.

1.2 Study Rationale

Clinical Significance

There is intense interest in the development of PARP inhibitors as drugs for use in cancer therapy. At least 8 major pharmaceutical companies (Tesaro, AbbVie, Astra-Zeneca, BioMarin, Clovis, Eisai, Inotek, Teva) have PARP inhibitor programs with interest in developing indications in cancer therapy (41). Consistent with an important role for PARP in modulating HR, promising single agent activity has been observed in pre-clinical and early clinical trials with PARP inhibitors as monotherapy in BRCA1- or BRCA2-deficient tumors (35, 36, 42, 43). Our group has demonstrated that addition of veliparib to TMZ therapy can profoundly prolong survival in a subset of GBM xenograft lines when tested in an orthotopic therapy evaluation model (44). Collectively, these exciting results suggest that PARP inhibitors can be safely combined with cytotoxic agents, and in appropriately selected patients, the combination of PARP inhibitors with chemotherapy may provide significant clinical benefit.

The combination of veliparib with TMZ has been evaluated in several clinical trials. In a Phase II clinical trial of heavily pre-treated colorectal cancer, the combination of TMZ (150 mg/m2 days 1-5) and veliparib (40 mg bid days 1-7) was well tolerated with only 5 of 47 patients having adverse events (myelosuppression) (45). Similarly, in previously treated metastatic breast cancer, modest rates of thrombocytopenia were observed with TMZ (150 mg/m2 days 1-5) combined with veliparib at 40 mg bid, and very low rates when veliparib was reduced to 30 mg bid days 1-7 (40). The ABTC 0801 trial evaluated the combination of veliparib with both concurrent radiation/TMZ and adjuvant TMZ in newly diagnosed GBM patients. In this study, the combination of veliparib given daily for 6 weeks with RT/TMZ or given daily for weeks 1, 3 and 5 of RT/TMZ was poorly tolerated with significant myelosuppression (personal communication, M. Prados). The distinct difference between the ABTC experience in GBM patients and the former colorectal and breast cancer trials is the protracted dosing concomitant with TMZ during radiation in the GBM trial. As described below, we also have observed increased toxicity with protracted combination schedules of veliparib and TMZ in animal models. Therefore, we anticipate that limiting veliparib dosing to the adjuvant TMZ treatment phase in newly diagnosed GBM patients should be well tolerated based on the previously published trials with colon cancer and breast cancer.

As described below, the extent of survival benefit observed in our preclinical data is unprecedented with the survival benefit of TMZ therapy nearly doubled when combined with ABT888 in a subset of xenograft models. Over half of the TMZ naïve xenograft lines harboring MGMT promoter hypermethylation had a significant survival extension with combined therapy, while none of the MGMT unmethylated tumors had a clinically relevant benefit. We believe these data provide a robust rationale for using MGMT hypermethylation as an enrollment criteria for the proposed trial and that the combination therapy has a strong likelihood of providing a clinically meaningful survival benefit in treated patients.

1.3 Relevant Data

Preliminary Data

Mayo GBM xenograft model system

Pre-clinical novel therapeutic testing traditionally has been performed using tumor cell lines maintained in cell culture for many years that have significantly genetically diverged from the derivative patient tumor. In contrast, the Mayo GBM panel of 65 xenograft lines was established by implanting patient tumor specimens directly into the flank of nude mice and maintained by serial transplantation. Using this method, key genetic and molecular features of the original patient tumor are preserved, including EGFR amplification (46) and MGMT promoter methylation status (47). Our laboratory has extensive experience in testing traditional and novel therapies using this xenograft model (48-56). Specifically relevant to this application, a clinically relevant dosing schedule of TMZ was tested in 20 xenograft lines (47, 57, 58), and consistent with multiple clinical studies, MGMT promoter methylation in our GBM xenograft model was highly associated with TMZ sensitivity as compared to non-methylated tumors ($p=0.008$, rank-sum test). Moreover, for a subset of xenografts in which patients received TMZ at some point during their clinical care, there was a close correlation between the clinical response and xenograft sensitivity to TMZ (47). Collectively, these data highlight the high degree of clinical relevance of the Mayo GBM xenograft panel for evaluating novel TMZ-sensitizing strategies.

Initial Studies with veliparib in Combination with TMZ and RT

PARP inhibitors are potent chemo-sensitizing agents, and in anticipation of developing a clinical trial in GBM, we obtained veliparib from CTEP as part of a pre-clinical LOI solicitation. The survival evaluation of combinations of veliparib with TMZ and/or RT was now been completed in 11 primary GBM xenograft lines. Ten xenograft lines were derived from TMZ-naïve GBM tumors, one from a recurrent GBM after failing TMZ therapy (GBM46R), and all have been passaged exclusively in nude mice prior to testing (46, 47). Of these primary lines, GBM6, GBM28, GBM43 and GBM79 are unmethylated within the MGMT promoter and express high levels of MGMT mRNA and protein. GBM5, GBM12, GBM22, GBM39, GBM46R, GBM59, and GBM63 are MGMT promoter hypermethylated and do not express appreciable MGMT levels. GBM28 has monosomy of Chromosome 10, and during serial passage the remaining allele of MGMT was deleted as demonstrated by PCR and western blotting such that later generation GBM28 tumors are deficient in MGMT. For clarity, the early passage GBM28 lines are denoted as GBM28A and late passage GBM28 (after MGMT deletion) are denoted as GBM28B. Because we have cryopreserved specimens from the pre- and post-deletion event, these paired tumor sub-lines are useful for examining the importance of MGMT expression. All of the pre-clinical studies shown below were performed using radiation and TMZ doses and schedules designed to closely mimic the typical clinical usage of TMZ, and all of the key studies were performed using an intracranial therapy evaluation model. Thus, the studies presented below provide a highly clinically relevant data set upon which the clinical trial design proposed is based.

We initially published our results with the combination of veliparib, TMZ and radiation in 2009 with specific focus on 2 MGMT methylated lines (GBM12 and GBM22) (44). To model clinical treatment paradigms, veliparib was combined both with RT/TMZ (2 Gy x 2 weeks and low-dose daily TMZ). Veliparib markedly enhanced the survival of mice with GBM12 orthotopic tumors treated with RT/TMZ with a 170 day increase in median survival. In an independent experiment with GBM12, the combination of veliparib with adjuvant dosing of TMZ (50 mpk/day, days 1-5 every 28 days) for 3 cycles significantly extended median survival for the combination treatment compared to TMZ alone by 130 days (data not shown). In GBM22, the combination

of RT and TMZ was highly efficacious, and the addition of veliparib did not further enhance the efficacy of combined therapy. However, veliparib combined with TMZ in GBM22-bearing mice resulted in a significant improvement in survival compared to TMZ alone. The extent of survival prolongation seen in these studies is profound in comparison to the efficacy of other novel therapeutic agents in our xenograft models (RAD001, erlotinib, enzastaurin) (50, 52), and we believe that the extent of benefit observed in these studies likely will translate into clinically meaningful survival benefits in at least a subset of GBM patients. Based on these results, we embarked on a series of studies, supported by an NIH RO1, designed to define the optimal schedule for combining TMZ and veliparib and to define a preliminary biomarker that could be used to enrich for a population of patients most likely to benefit from combination therapy.

Optimal dose/schedule of TMZ and veliparib

There is considerable interest in defining whether more dose-intensive TMZ dosing schedules might provide a clinical benefit in GBM patients. There are several clinical dosing regimens that have been explored including standard (TMZ 150-200 mg/m2 days 1-5 every 28 days), dose-dense (TMZ 100 mg/m2 days 1-21 every 28 days) and metronomic (TMZ 75 mg/m2 continuously). Although recent results from the RTOG 0525 clinical trial suggests that dose-dense TMZ therapy does not provide a significant benefit as compared to standard TMZ therapy in GBM patients, the greater exposure to TMZ-induced lesions might provide a benefit when combined with continuous PARP inhibition. Therefore, we performed a study in GBM12 orthotopic xenografts to compare the efficacy of standard and dose-dense TMZ dosing schedules alone and in combination with veliparib. In comparing the 2 TMZ dosing regimens without veliparib, dose-dense therapy was associated with longer survival as compared to standard dosing (data not shown). However, in combination regimens, veliparib significantly enhanced the efficacy of standard TMZ dosing ($p<0.001$) while the combination with dose-dense TMZ therapy was associated with a number of early toxicity-related deaths such that the combination was no better than dose-dense TMZ alone ($p=0.58$). In comparing the 2 combination regimens, there was no difference in survival for the dose-dense TMZ/veliparib compared with standard TMZ/ABT ($p=0.23$). These data suggest that the combination of veliparib with either standard or dose-dense TMZ may be efficacious, but that veliparib combined with TMZ dose-dense therapy may be associated with increased toxicities in mice.

The efficacy of dose-dense therapy was modeled in a second GBM tumor line that in retrospect was defined as MGMT deleted (GBM28B). In this experiment, dose-dense and standard TMZ dosing was compared alone and in combination with veliparib. In contrast to GBM12, there was no significant difference in the efficacy of standard or dose-dense TMZ monotherapy (data not shown). Veliparib combined with standard TMZ was associated with improved survival benefit as compared to monotherapy ($p=0.04$), while veliparib combined with dose-dense TMZ was no different than either standard or dose-dense TMZ monotherapy ($p=0.73$). In comparing survival on the 2 combination regimens, standard TMZ/veliparib was equivalent to dose-dense TMZ/ABT ($p=0.34$) dosing. Collectively, the GBM12 and GBM28B data suggest that veliparib combined with the standard TMZ dosing schedule (Days 1-5 every 28 days) is at least equally efficacious to a combination of veliparib with dose-dense TMZ.

The optimal duration of veliparib therapy in combination of TMZ is unknown. Since veliparib has a relatively short half-life and should reach steady state quickly after initiation of therapy, we reasoned that pre-loading with veliparib prior to TMZ was not necessary. However, DNA damage incurred by TMZ can persist for several days following cessation of TMZ therapy, and therefore we tested whether extending veliparib therapy for 1 week following completion of a 5 day course of TMZ would provide a significant survival benefit. Using GBM12 as a model, mice were randomized to 2 cycles of therapy.

There was no significant difference in survival for mice treated with TMZ (days 1-5 every 28 days x 2 cycles) concurrent with veliparib (Days 1-5 x 2 cycles) or concurrent and extended veliparib (Days 1-12 x 2 cycles) (p=0.47). These data suggest no compelling rationale to significantly extend veliparib dosing beyond the completion of TMZ therapy during adjuvant cycles.

The brain penetration of veliparib was evaluated in the same nude mouse model. Following 5 days of treatment with veliparib, plasma and normal brain were harvested at for time points (0 hr, 0.5 hr, 2 hr, 6 hr) after the last dose. Analysis of these data demonstrates an average concentration maximum of 1.2 µM in plasma and 0.27 µM in normal brain with a brain to plasma ratio of 0.23 µM. Area under the curve for plasma was 2.1 µM*hr and for brain was 0.86 µM*hr with a brain to plasma AUC ratio of 0.41. The half-life in plasma and brain are 2.7 hr and 3.4 hr respectively. These data demonstrate reasonable penetration of veliparib into the brain and are consistent with the observed efficacy in our orthotopic xenograft models

To summarize, the data presented above demonstrate robust TMZ sensitizing potential for veliparib combined with TMZ in 3 GBM xenograft lines that are deficient for MGMT expression. With no compelling data supporting combinations with dose-dense TMZ, we plan to test the combination of veliparib with standard TMZ dosing in the adjuvant setting.

Definition of an enrichment strategy

The data presented above demonstrate excellent sensitizing potential for veliparib combined with TMZ in 3 distinct GBM tumor lines that are inherently TMZ sensitive and provide a rationale for testing the combination in GBM. Published data suggest that PARP inhibition should also sensitize tumors that are resistant to TMZ. To test this concept, we evaluated the efficacy of TMZ in 4 MGMT unmethylated tumor lines that express high levels of MGMT (GBM6, GBM28A, GBM43 and GBM79). The combination of veliparib with standard TMZ dosing did not provide a clinically meaningful increase in survival with the maximum benefit of a 7 day prolongation in median survival seen in GBM6. Of specific note, in contrast to the benefit seen with the same treatment regimen in the MGMT deficient GBM28B line, there was no benefit for the combination in GBM28A, which expresses MGMT.

The efficacy of TMZ combined with veliparib was evaluated in a total of 8 xenograft lines that harbor MGMT promoter hypermethylation or lack MGMT expression. The data from all studies are summarized in **Table 1**. Overall, 4 of 8 tumor lines significantly benefited from combined veliparib + TMZ therapy as compared to TMZ alone, and in these 4 lines, combination therapy was associated with an approximate doubling in the median survival compared to TMZ therapy alone. Of interest, the inherently TMZ resistant GBM46R line, which was derived from a patient at the time of recurrence after progression on TMZ therapy, the combination of veliparib+TMZ was no better than TMZ alone. Collectively, these data suggest that MGMT promoter hypermethylation in previously untreated GBM may enrich for a population of tumors most likely to benefit from veliparib combined with TMZ.

	placebo	ABT-888	TMZ*	TMZ+ABT*	*p-value
MGMT unmethylated					
GBM6	41	NA	58	65	<0.001
GBM28A	26	NA	33	34	0.24
GBM43	14	NA	62	39	0.43
GBM79	31	NA	32	31	0.02
MGMT methylated					
	placebo	**ABT-888**	**TMZ***	**TMZ+ABT***	***p-value**
GBM5	103	106	237	286	0.27
GBM12	31	28	79	154	0.01
GBM22	20	19	58	94	0.03
GBM28B	34	37	98	188	0.04
GBM39	28	30	138	288	0.02
GBM46R	34	38	36	48	0.78
GBM59	48	52	96	174	0.13
GBM63	82	95	262	276	0.18

Table 1: Summary of veliparib/TMZ versus TMZ alone studies done in both MGMT unmethylated and MGMT hypermethylated tumors using an orthotopic therapy model and conventional TMZ dosing (50-66 mg/kg PO days 1-5 every 28 days). The median survival for each treatment is reported in columns 2 through 5. * p-values relate to the comparison of TMZ versus TMZ + ABT-888.

GBM12 and GBM28B do not express appreciable levels of MGMT, with MGMT expression suppressed by promoter hypermethylation in GBM12 and loss of both alleles of MGMT during routine heterotopic passage in GBM28. To evaluate the impact of MGMT expression on the sensitizing effects of veliparib, MGMT was ectopically overexpressed in both GBM12 and GBM28B via lentiviral transduction, and the efficacy of veliparib combined with TMZ was evaluated as described above. For GBM28, genomic PCR for MGMT in archived tumor samples defined the MGMT loss event happened by generation 13. While the initial study in GBM28B (MGMT deleted) was performed in a tumor from passage 28, the study in GBM28B was repeated with a passage 17 tumor (4 passages after loss of MGMT), and similar to the previous study with GBM28B, there was a clear TMZ-sensitizing effect of veliparib (p=0.05). To specifically address the importance of MGMT on the sensitizing effects of veliparib, this 'early' GBM28B line was transduced with a pSIN-MGMT lentiviral construct. As expected, over-expression of MGMT rendered GBM28B resistant to TMZ and more strikingly, veliparib was no longer effective as a TMZ-sensitizing agent (p=0.19;). A similar effect was observed in GBM12 where TMZ alone or in combination with veliparib was completely ineffective in the setting of MGMT overexpression (**Figures 1A** and **1B**). Collectively, these data demonstrate that in TMZ-naïve GBM tumors, lack of MGMT expression is critically important for effective sensitization by veliparib, and the mechanisms responsible for this effect are currently being investigated.

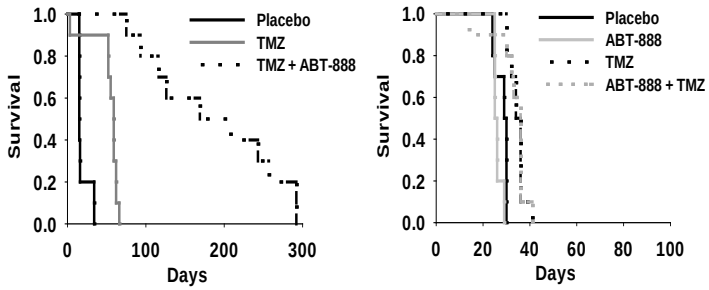

Figure 1: Influence of MGMT expression on sensitizing effects of veliparib. The efficacy of TMZ alone and in combination with veliparib was tested in A) parental GBM12 and B) GBM12 transduced with pSIN-MGMT. * p-values relate to the comparison of TMZ versus TMZ + veliparib.

The combination of veliparib and TMZ also was studied in models of acquired TMZ resistance. For our initial studies, a single mouse with either GBM12 or GBM22 flank tumors were subjected to escalating doses of TMZ until the resulting tumors became highly resistant to TMZ therapy (the resulting tumors are denoted as GBM12TMZ and GBM22TMZ, respectively). GBM12TMZ is resistant due to MGMT over-expression while GBM22TMZ is resistant through non-MGMT dependent mechanisms. In contrast to the marked sensitizing effects observed in the parental GBM12 and 22 tumor lines, the combination of veliparib and TMZ was no better than TMZ alone in either GBM12TMZ and GBM22TMZ **(**Clarke et al.,2009)**.**

The heterogeneity of resistance emergence in GBM12 was studied in a second study in which mice implanted with GBM12 flank tumors were randomized to therapy with placebo, TMZ, and veliparib+TMZ. Tumor growth was monitored thrice weekly and tumors larger than their endpoint were cryopreserved and analyzed for mechanisms of resistance. Consistent with our studies in the intracranial therapy model, therapy with veliparib + TMZ was more effective at delaying tumor growth as compared to TMZ alone. In an analysis of resistance mechanisms from TMZ-treated tumors, 2 of 10 tumors had high-level mRNA MGMT expression. To test whether MGMT over-expression was linked to TMZ-resistance development in this model, one tumor without MGMT expression (animal #5920) and one tumor with high level MGMT expression (animal #3080) were grown as neurospheres and the efficacy of TMZ alone and in combination with the MGMT inhibitor O6BG was tested in a neurosphere formation assay. O6BG profoundly enhanced the efficacy of TMZ in the MGMT over-expressing line (#3080), but not in the MGMT low line (#5920). Since O6BG is a selective inhibitor for MGMT activity, these data confirm that TMZ resistance in the #3080 tumor is mechanistically lined to MGMT over-expression, while the mechanism of TMZ resistance in #5920 is currently unknown, but definitively not related to MGMT.

The efficacy of TMZ and veliparib was evaluated in these 2 TMZ resistant GBM12 sub-lines in a flank tumor growth assay. Similar to the initial GBM12 flank study, mice implanted with tumor cells were randomized to therapy with placebo, veliparib, TMZ or TMZ + veliparib. Both the #3080 and #5920 tumor sub-lines were highly resistant to TMZ and TMZ + veliparib. In contrast to the GBM12 flank tumor study from which these tumor sub-lines were derived, these data support the idea that veliparib is ineffective in TMZ resistant tumor lines.

In summary, we have tested veliparib combined with TMZ in 11 primary GBM xenograft lines. The combination was effective in 4 of 7 lines that are inherently sensitive to TMZ and are MGMT promoter hypermethylated with associated low MGMT expression. In contrast, the combination was ineffective in 4 inherently TMZ-resistant lines with MGMT promoter hypomethylation and high level MGMT expression. In one model (GBM28), loss of MGMT expression in a sub-line was associated with increased sensitivity to TMZ and effective sensitization with the addition of veliparib to TMZ therapy. Conversely, development of TMZ resistance, by either of 2 mechanisms in a tumor line (GBM12) originally sensitive to ABT/TMZ resulted in loss of efficacy for the combination. Collectively, we have tested 9 TMZ resistant xenograft models, and the combination of TMZ and veliparib was ineffective in all of them. In contrast, in 7 TMZ-sensitive xenograft models, 4 likely benefited from combination therapy. Moreover, in the MGMT non-expressing lines GBM28B and GBM12, in which the combination of TMZ and veliparib was effective, specific restoration of MGMT expression resulted in loss of the sensitizing effects of veliparib. On the basis of these in vivo data, we hypothesize that only TMZ sensitive tumors lacking MGMT expression will benefit from a combination strategy with veliparib and TMZ.

Molecular studies have defined 2 major mechanisms of TMZ resistance: MGMT over-expression and mutational inactivation of MMR. Promoter hypermethylation is a major mechanism of transcriptional repression of MGMT in GBM, and clinical data from RTOG 0525 and EORTC 22981 both have demonstrated that MGMT promoter hypermethylation is associated with superior survival for newly diagnosed GBM patients treated with radiation and temozolomide. While there are undoubtedly other mechanisms that modulate MGMT expression and inherent TMZ sensitivity, we hypothesize that MGMT promoter hypermethylation can be used to highly enrich for a population of patients most likely to benefit from PARP inhibitor therapy combined with TMZ. While MMR mutation is a major mechanism of TMZ resistance in colon cancer and likely in a subset of recurrent GBM, genome-wide mutational analyses performed by the TCGA in TMZ-naïve GBM samples suggest a low rate of MMR mutation in newly diagnosed GBM. Thus, based on the known mechanisms of inherent TMZ resistance in GBM, we propose to use only MGMT promoter hypermethylation to enrich for patients most likely to respond to combination therapy.

Two potential strategies for patient selection were entertained for this randomized Phase II/III clinical trial. In one design, all patients would be enrolled on the trial and the MGMT methylation status could be used as a stratification factor or simply in the analysis of patient outcomes. With careful attention to the anticipated accrual of MGMT promoter hypermethylated tumors, the trial could be powered specifically to test the hypothesis that MGMT promoter hypermethylation will select for a subset of patients most likely to respond to veliparib in combination with TMZ. A second design would limit enrollment only to patients with MGMT promoter hypermethylation (approximately 30% of newly diagnosed GBM patients based on results from RTOG 0525). On the basis of our preliminary animal data demonstrating a lack of benefit for inherently TMZ resistant tumors and those tumors with MGMT expression, this design will maximize potential clinical benefit while limiting the number of patients exposed to the risk of adverse events related to veliparib therapy. With the goal of maximizing patient benefit in the current trial design, we have elected to pursue the latter trial design, and only patients with tumor MGMT promoter hypermethylation will be enrolled on this Phase II/III clinical trial.

The RTOG is currently testing veliparib combined with metronomic TMZ therapy in recurrent GBM that have failed TMZ therapy in a randomized Phase II study (RTOG 0929). Based on our preclinical data discussed above, we would argue that a negative result on RTOG 0929 would not negate the rationale for our currently planned study in TMZ-naïve patients with MGMT promoter hypermethylation. In fact, if RTOG 0929 is negative, this would further support the

translational relevance of the pre-clinical studies presented herein. Thus, we do not believe that a go/no-go decision for the current trial proposal should be linked to the future results from RTOG 0929.

The pharmacokinetics (PK), safety and tolerability of veliparib alone and combined with temozolomide have been studied in multiple clinical trials. Initial PK studies demonstrated no significant interactions between veliparib and temozolomide, and no effect of food on the bioavailability of veliparib. In an initial Phase I clinical trial, dose escalation of veliparib was well tolerated up to 40 mg PO BID in combination with TMZ at 200 mg/m2. In a subsequent expansion cohort, thrombocytopenia or neutropenia was minimized in the first cycle by starting TMZ at 150 mg/m2 and then escalating to 200 mg/m2 if well tolerated. In combination with a second Phase I trial, the recommended dosing regimen for Phase II testing is veliparib 40 mg BID given on Days 1-7 in combination with TMZ 150 mg/m2 Days 1-5 in cycle 1 and if no significant hematologic toxicity is encountered, to escalate TMZ dosing to 200 mg/m2 in cycle 2 through cycle 6. With this dosing regimen, a randomized Phase II clinical trial in melanoma patients compared TMZ alone to combinations with 20 or 40 mg veliparib BID. In comparison to TMZ therapy alone, the incidence of Grade 3/4 thrombocytopenia and neutropenia were significantly increased with TMZ in combination with veliparib. Other common effects, that were similar in incidence to TMZ alone, included nausea, vomiting, constipation, anorexia and fatigue. The combination regimen also has been tested in a randomized trial compared to pegylated doxorubicin in recurrent ovarian cancer and now is accruing patients for an open label Phase II clinical trial and a randomized phase II trial in BRCA 1/2 mutant metastatic breast cancer patients. While cyclical dosing of veliparib and TMZ in these Phase II studies is well tolerated, a Phase I study of daily veliparib combined with radiation and daily temozolomide for 6 weeks in newly diagnosed GBM was poorly tolerated even when veliparib was dosed at 10 mg BID. Based on this latter experience, the current trial will test the combination of veliparib 40 mg BID and TMZ (150 to 200 mg/m2) only during adjuvant therapy following completion of conventional daily radiation combined with daily TMZ.

There is limited data on the efficacy of veliparib combined with TMZ. In a Phase I study of 42 patients with solid malignancies, there were 2 confirmed partial responses and 3 unconfirmed partial responses. In a Phase IB study of the combination in castration refractory metastatic prostate cancer, 2 of 25 patients had a biochemical partial response with a reduction in PSA. In the randomized Phase II melanoma study, there was no statistically significant difference for overall response rate, progression-free survival or overall survival between those patients treated with TMZ only, TMZ + veliparib 20 mg BID or TMZ + veliparib 40 mg BID. Similarly, in a preliminary analysis of a Phase II ovarian cancer trial, there was no difference in overall response rate for patients treated with TMZ + veliparib compared to pegylated liposomal doxorubicin. While the data for the latter trial is not mature and several other Phase II trials have not reached maturity, the limited efficacy observed in these studies using an unselected population of patients underscores the potential importance of enriching for a population of patients that are most likely to benefit from combination therapy. Based on extensive pre-clinical data used to develop the current trial, only newly diagnosed GBM patients with tumor MGMT promoter hypermethylation will be eligible to enroll on this trial. Using this enrichment strategy, we believe the current trial has a much greater chance for success in defining an efficacious regimen for a subset of patients with GBM.

Pseudoprogression (PsP) is a radiographic finding of apparent worsening of a tumor on MRI following radiation and temozolomide therapy in the setting of a patient that is clinically stable and on stable doses of steroids. Although the pathophysiology of PsP has not been clearly delineated, the effect likely is a manifestation of tumor cytotoxicity following therapy. Consistent with this idea, there may be an increased frequency of PsP in patients with MGMT promoter hypermethylation, and the survival for patients with PsP appears to be superior to those

without PsP (71). The RANO criteria have defined PsP as occurring within the first 12 weeks following completion of radiation therapy (59). However, there are isolated reports of PsP or treatment-related necrosis happening beyond this 12 week window (68; 69, 70) and in a preliminary report of patients treated with a dose-intensive CCNU/TMZ adjuvant chemotherapy regimen, 3 of 8 patients with MGMT promoter hypermethylation experienced PsP at times substantially later than the 12 week window (67). Since the current trial is enrolling only MGMT methylated patients, we anticipate a higher than typical rate of PsP, and patients suspected of having PsP are eligible for enrollment on this trial. The testing of a TMZ-sensitizing strategy with veliparib may lead to an even higher rate of PsP, and these events may occur later than the typical 12 week window. Because the incidence of PsP indicates a favorable therapeutic response, continued therapy with veliparib/placebo combined with TMZ is critical in this setting. Thus, for the purposes of this trial, patients with typical radiographic and clinical findings consistent with pseudoprogression should remain on study even if the initial indication of PsP occurs beyond the RANO-defined cut-off of 12 weeks.

2.0 Objectives

2.1 Primary objective

Test whether the experimental combination of ABT-888 (veliparib) combined with TMZ, compared to the control of placebo combined with TMZ, significantly extends overall survival in newly diagnosed GBM patients with tumor MGMT promoter hypermethylation.

2.2 Secondary objectives

2.2.1 Test whether the experimental treatment significantly extends progression-free survival.

2.2.2 Test whether the experimental treatment improves objective tumor response.

2.2.3 Test whether the experimental treatment is associated with significantly greater rates of grade 3 or higher adverse events.

2.3 Correlative Science Objectives

2.3.1 Evaluate the utility of dynamic susceptibility contrast (DSC) and diffusion weighted imaging (DWI) MRI techniques in defining time to progression in the setting of a large multi-institutional clinical trial.

2.3.2 Test the concordance between site-determined MGMT methylation status and central laboratory determination of MGMT status in cases with local testing.

2.3.3 Evaluate whether genetic or epigenetic alterations in DNA repair or replication genes are associated with overall survival, progression-free survival, and objective tumor response.

2.3.4 Test whether polymorphisms in MGMT, PARP1, or other DNA repair proteins, are associated with overall survival, progression-free survival, objective tumor response, or rates of grade 3 or higher adverse events.

3.0 Patient Selection

For questions regarding eligibility criteria, see the Contact Information page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding

whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with uncontrolled infection or patients with HIV with immunosuppression should be definitively excluded.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years. Patients treated for prior brain tumor, nasopharynx or sinus cancer with a previous course of radiation in which significant dose to the brain was delivered may not participate in this trial.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

3.2 Pre-Registration Eligibility Criteria

3.2.1 **Histologic documentation:** Newly diagnosed WHO Grade IV intracranial glioblastoma or gliosarcoma. GBM with oligodendroglial features are NOT PERMITTED in this study if they are 1p19q codeleted. Sites submitting GBM with oligodendroglial features will be asked to provide results of 1p/19q codeletion status.

3.2.2 Sufficient tissue available for central pathology review and MGMT methylation status evaluation.

3.2.3 Age ≥ 18 years of age

3.2.4 Patients who have had a local MGMT testing that is unmethylated are not allowed to participate.

3.3 Registration Eligibility Criteria

3.3.1 Tumor MGMT promoter hypermethylation determined by central testing at MD Anderson.

3.3.2 Confirmation by central pathology review of WHO Grade IV glioblastoma or gliosarcoma.

3.3.3 Required Lab Values:

Required Initial Laboratory Values:
(Within 14 days prior to study registration)

Absolute neutrophil count (ANC)	≥ 1500 cells/mm^3
Platelets	≥ 100,000 cells/mm^3
Creatinine	≤ 1.5x ULN
Bilirubin [1]	≤ 1.5x ULN
ALT	≤ 3 x ULN
AST	≤ 3 x ULN

[1] Unless patient has Gilbert's disease

3.3.4 ECOG Performance Status ≤ 2

3.3.5 Measurable disease and/or non-measurable disease as defined in Section 11.0.

Extent of resection: Patients with complete resection, partial resection, or biopsy are eligible.

3.3.6 Progression: Patients deemed to have progressive disease based on clinical deterioration after chemoradiation or radiographic progression outside of the radiation field are not eligible. (See Section 11.4.3.2 for definition of clinical deterioration). Patients deemed to have pseudoprogression (as defined in Section 11.4.3.2) are eligible.

3.3.7 Prior Treatment

- Must have completed standard radiotherapy and concomitant TMZ therapy as defined in Appendix I and determined by the study oncologist.
- Besides concomitant TMZ with radiation, no other therapy (neo-adjuvant or adjuvant) can be given prior to study registration, including chemotherapy, biologics, immunotherapy, radiation therapy.

3.3.8 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects. **Females of childbearing potential must have negative urine or serum pregnancy test within 7 days of registration but before start of treatment.** A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.3.9 Concomitant Medications:

- Patients receiving anticoagulation should be on stable dose 2 weeks prior to registration.

3.3.10 Comorbid Conditions: Patients are unable to participate due to the following:

- Seizure disorder that is uncontrolled at the time of registration. The definition of controlled seizures is patients must be without seizures for at least 10 days prior to registration.
- Grade 3 or 4 thromboembolic disease within 6mo of registration
- Known history of prolonged QT syndrome

3.3.11 No history of major surgery ≤ 14 days prior to registration

4.0 Patient Registration

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed Statement of Investigator Form (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed Supplemental Investigator Data Form (IDF)
- a completed Financial Disclosure Form (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the CTEP Investigator Registration Help Desk by email at <pmbregpend@ctep.nci.nih.gov>.

4.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

4.3 CTSU Site Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB 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. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU

Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

4.3.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A071102 protocol page located on the CTSU members' website. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Group name) link to expand, then select trial protocol # A071102
- Click on the Site Registration Documents link

4.3.2 Requirements for A071102 Site Registration

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

4.3.3 Submitting Regulatory Requirements

Submit completed forms along with a copy of your IRB Approval (for sites not participating via the NCI CIRB), Model Informed Consent (for sites not participating via the NCI CIRB), and any other required documentation (see above) to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4.3.4 Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

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 at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

4.3.5 Credentialing

See Section 15.0 for credentialing requirements

4.4 Registration Requirements

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.

4.5 Pre-registration

Patients may be pre-registered to this study on the basis of the diagnosis of glioblastoma or gliosarcoma made at the original institutions. All patients must submit ALL diagnostic H&E's and one tissue block. (See Section 6.0).

Submission of these samples for MGMT promoter methylation assessment is MANDATORY for all patients pre-registered to this study.

If a prior analysis of MGMT status at the treating institution revealed an unmethylated tumor status, these patients will not be eligible and MUST not be pre-registered. See Section 3.2.4.

4.6 Patient Registration/Randomization

4.6.1 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

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. A user manual is available for OPEN users on the CTSU site.

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

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol-specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.7 Registration to Correlative and Companion Studies

4.7.1 Registration to Substudies described in Section 14

There are three substudies within Alliance A071102. These correlative science studies **must be offered to all patients** enrolled on Alliance A071102. These substudies do not require separate IRB approval. The substudies included within Alliance A071102 are:

- **DNA Extraction from Tissue, Alliance A071102-ST1** (Section 14.1)

  Extracted DNA from the tumor block in excess of that required for MGMT analysis, will be used for future correlative studies and is an optional portions of this sub-study.

- **DNA Extraction from Blood, Alliance A071102-ST2** (Section 14.2)

  Extracted DNA from a blood sample for germ-line DNA will be used in conjunction with the tumor DNA for future correlative studies and are optional portions of this sub-study.

  For patients who consent to participate in the germline DNA analysis, a blood sample must be submitted.

- **Analysis of advanced MR imaging, Alliance A071102-IM** (Section 14.3)

4.8 Stratification (or Grouping) Factors and Treatment Assignments

- Patients will be stratified by age group: <70 vs. ≥70 years
- ECOG performance status 0-1 vs. 2
- Extent of resection gross total resection vs. subtotal resection or biopsy

5.0 Study Calendar

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 14 DAYS before registration: All laboratory studies, history and physical.

	Prior to Registration	**Days 1 of each cycle (10)**	**Post treatment follow up**
Tests & Observations			
History and physical, weight, PS	X	X(1)	X(11)**
Height	X		
Pulse, Blood Pressure	X	X(1)	
Adverse Event Assessment		X(1)	X**
Patient Medication Diary (See Appendix VI)		X(2)	
Fatigue/Uniscale Assessment (See Appendix IV)	X(3)	X(1)	X**
Mini Mental State Examination (See Appendix V)	X(13)		
Laboratory Studies			
Complete Blood Count, Differential, Platelets	X	X(4)	X**
Serum Creatinine,	X	X(5)	
Albumin, glucose	X	X(5)	
AST, ALT, Alk. Phos., Bili	X	X(5)	X**
Serum or Urine HCG	X(6)		
Staging			
Central Pathology review and MGMT testing for eligibility	X(7)		
Brain Imaging (MRI or CT) (8)	X(9)	X(12)	X(11)
Correlative studies: For patients who consent to participate			
Blood samples (See Section 6.0 and 14.2)	Baseline (Before start of treatment)***		
Residual Tissue (See Section 6.0 and 14.1)			

** Visit to be performed 21-35 days after completion of treatment.

*** It is strongly preferred that the research blood sample is drawn prior to start of study therapy, however, it is acceptable to submit within 60 days of registration to the treatment trial.

1 To be completed once every 28 days +/- 7 days.
2 The diary must begin the day the patient starts taking the medication and must be completed and returned to the treating institution with each cycle. Medication reconciliation should be performed on each day 1 visit: Patients should return remaining pills from the last cycle and this should be reconciled.
3 To be completed ≤ 21 days prior to treatment, see Appendix IV.
4 CBC to be completed +/- 3 days of Day 1 for each cycle and on day 14 +/- 3 days for each cycle.
5 To be completed +/- 7 days of each cycle start.
6 For women of childbearing potential (see Section 3.3.9). Must be done ≤ 7 days prior to registration and prior to starting treatment.
7 Central Pathology Review and MGMT testing can be done at any time as long as the patient is randomized to treatment within 28 to 42 days after completion of RT/TMZ
8 All imaging must be submitted to the Imaging and Radiation Oncology Core within 6 months of acquisition. Images must be submitted from the following time points: baseline (pre and post radiation) and while on treatment. For patients who have progressive disease, submit one scan after confirmed progression and no further scans. For patients who go off study for reasons other than progression (i.e., toxicity) please continue to submit images until progression.
9 Must be done both prior to radiation and 21-42 days after completion of radiation and temozolomide.
10 For patients who develop progressive disease (defined in Section 11) while on treatment, they will be followed as per the survival and disease follow up. For patients who go off-study treatment for reasons other than progressive disease, please see Section 12.1.3.
11 Physical exams and MR are required every 3 months (+/- 14 days) for the first 3 years, then every 6 months (+/- 28 days) in years 4 and 5, or until confirmed progression, after which one additional MR is to be submitted; thereafter, survival calls every 6 months only are required. See Section 11.4.3.1.
12 MR is required every 2 months (+/- 7 days) during treatment with temozolomide plus veliparib/placebo.
13 Report score only in Rave.

6.0 Data and Specimen Submission

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster 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. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. 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 in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis and progression. Supporting documentation will include:

- Pre-registration operative note, pathology report, local MGMT testing (if performed), and radiation summary (if complete during the pre-registration timeframe)
- Baseline initial consult note, post radiation visit note, imaging report, and radiation summary (if not already submitted at pre-registration)
- Progression pathology report (as applicable), operative report (as applicable), imaging report, clinic note

6.2 Pathology Considerations: Tissue Specimen Collection and Submission

For all patients pre-registered to Alliance A071102:

Real time pre-registration histopathology review will be conducted on the diagnostic tissue (biopsy and/or surgery) to confirm the diagnosis of Glioblastoma or Gliosarcoma (WHO grade IV). Glioblastoma <u>with oligodendroglial features are NOT PERMITTED in this study if they are 1p19q codeleted. Sites submitting GBM with oligodendroglial features will be asked to provide results of 1p/19q codeletion status.</u> ALL original diagnostic H&E slides used to make the diagnosis should be clearly labeled and forwarded along with at least 1 FFPE block

containing tumor **as soon as possible after surgery for pre-registration. The submission of these samples for histopathology review is required for all patients pre-registered to this study.**

MGMT promoter hypermethylation will be used as an integral biomarker and key entry criteria for enrollment on this trial. The central reading pathologist will select the block suitable for analysis, have sections cut, and then ship the sections to the Alliance Biorepository at Mayo Clinic for processing, where they will be forwarded to MD Anderson to Dr. Sulman's lab for testing. The MGMT results will be returned to the treating site in real-time so that those patients can be registered for the study if they are MGMT methylated. Typical turnaround time for Central Pathology Review and MGMT testing is within 21 calendar days of receipt of tissue at the Alliance Biorepository at Mayo Clinic.

For those patients in whom MGMT status is known and methylated, from the treating site (assessed by a CLIA-certified lab using either MGMT qMS-PCR or pyrosequencing), but central review is negative, **patients are not eligible to participate**. A detailed description of the assay is provided in Appendix VII. **Submission of these samples for MGMT promoter methylation assessment is required for all patients pre-registered to this study.**

	Pre-registration	≤ 120 days of registration	At recurrence***	Storage/ Shipping conditions	Submit to:
Mandatory for all patients registered to A071102: (parent study)					
ALL diagnostic H&E slides from original Diagnosis	X				Alliance Biorepository at Mayo Clinic
One paraffin block containing at least 1 cm^2 of viable tumor *, **, ****	X				Alliance Biorepository at Mayo Clinic
For patients registered to A071102-ST1, submit the following: Optional					
ALL diagnostic H&E slides from ***recurrent tumor***			X(2)		Alliance Biorepository at Mayo Clinic
One paraffin block from ***recurrent tumor* ** ***			X(2)		Alliance Biorepository at Mayo Clinic
For patients registered to A071102-ST2, submit the following:					
Whole blood EDTA/lavender top tube (3)		1 x 10 mL		Cool pack/ship over night	Alliance BAP at Mayo Clinic

1 Submit as soon as possible after surgery at pre-registration. Pre-registration requirement, confirmation of diagnosis through central review.

2 Submit at the time of recurrence if new surgery is performed.

3. For future genetic testing as described in Section 14.1.

Note: It is strongly encouraged that whole blood samples are collected prior to the initiation of study treatment. However, sample collection and registration to the –ST2 sub-study may take place within 60 days of registration to the treatment trial.

* This can be present in a single paraffin block or be the composite of multiple blocks in cases with small tumor content in each block

** **If an institution is unable to provide a tissue block**, cut 13 five-micron sections and mount on charged glass slides. H&E stain the first slide. Slides need to be cut with a new blade and using a fresh water bath to avoid contamination. **Label the slides with Alliance patient ID number, accession number, and order of sections.** These H&E slides will be reviewed centrally under the research base's protocol for assessing tissue quality before being forwarded to MD Anderson Sulman's lab for MGMT promoter methylation testing. For samples containing less than 1 square cm of tumor tissue, multiple sections could be mounted onto each slide or additional slides can be provided to ensure that the appropriate amount of tumor tissue is available. **Do not bake or place covers slips on the slides.**

*** Progression samples may be collected and submitted up to 3 months after recurrence.

****Residual tissue from MGMT testing will be banked if patients opt in.

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (A071102), Alliance patient number, patient's initials and date and type of specimen collected.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. **Extreme heat precautions should be taken when necessary.**

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

6.3 Tissue collection and processing for histopathology review

Consistent and accurate histologic grading is important for this study. Submission of ALL diagnostic H&E slides and at least 1 paraffin block from the original diagnosis is required for all patients enrolled to this study. Submission of diagnostic H&E slides and at least 1 paraffin

block at time of recurrence is required from patients who consent to optional substudy and experience tumor recurrence.

6.3.1 Central pathology review is required <u>prior</u> to registration.

ALL original diagnostic H&E slides used to make the diagnosis of glioblastoma or gliosarcoma should be clearly labeled and forwarded **as soon as possible after surgery for pre-registration.** If the original slides cannot be released, recut slides from ALL tumor blocks used to make the diagnosis are acceptable.

- If diagnostic slides and accompanying materials have been previously submitted to Dr. Caterina Giannini and associates, Mayo Clinic Rochester, for a consult review, fax a copy of this review to the Alliance Pathology Coordinator (507-266-7240) to verify diagnosis. The Pathology Coordinator will contact you to inform you if the patient is eligible based on histologic criteria. If the patient is eligible, all the H&E slides will still need to be forwarded according to shipping instructions below (see Sections 6.3.2-6.3.4).
- If a patient's surgery was at Mayo Clinic Rochester, you may call the Pathology Coordinator listed on the protocol Resource Page. The Pathology Coordinator will request a copy of the Surgical Pathology Report and determine patient block availability. After confirmation of block availability, the Pathology Coordinator will contact you to inform you if the patient is eligible. If the patient is eligible, you may proceed with registration via the eligibility checklist.

6.3.2 The diagnostic slide(s) and block(s) must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, patient initials, and study patient ID number.

6.3.3 <u>In order to assure prompt handling, please call the Alliance Pathology Coordinator at (507) 266-0724 to alert of the time/date sent and courier contracted.</u>

6.3.4 Ship all specimens and accompanying materials to the Alliance Operations Office:

Alliance Operations Office
Attn: PC Office (Study A071102)
RO_FF_03_24-CC/NW Clinic
200 First Street SW
Rochester, MN 55905

6.3.5 The Alliance Operations Office will forward the unstained slides for MGMT promoter methylation assessment to: Dr. Sulman's laboratory.

6.3.6 Banking of Residual Tissue After Mandatory Eligibility Tests Have Been Completed

With the patient's consent, residual paraffin blocks of primary and, when available, recurrent tissue obtained from tumor specimens may be sent to the Alliance Biorepository at Mayo Clinic.

The Alliance has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block.

Please contact the Alliance Biorepository at Mayo Clinic if additional assurances with your hospital pathology department are required.

The MGMT methylation assay requires DNA extraction from the tumor block, and DNA in excess of that required for the methylation assay will be sent from the Sulman laboratory to the Alliance Biorepository at Mayo Clinic.

6.4 Blood Submission

For patients who consent to participate, collect 10 mL of venous blood in lavender top (EDTA anticoagulant) vacutainer tube(s). The tubes should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping. The sample should be placed in a biohazard bag and shipped according to IATA guidelines the same day as the blood is drawn on a cold pack by overnight courier service to the Alliance Biorepository at Mayo BAP.

Note: It is strongly encouraged that whole blood samples are collected prior to the initiation of study treatment. However, sample collection and registration to the –ST2 sub-study may take place within 60 days of registration to the treatment trial.

Ship specimens to the following address:
BAP Freezer
ST SL-16 150 third street SW
Rochester, MN 55902
507-293-0065

Contacts
Roxann Neumann
Biospecimen
507- 538-0602

Ann Thorson
Biospecimen
507-284-0163

6.5 CT and MR Imaging Data Submission

Complete data sets in digital DICOM format, along with Alliance Adjunctive Data Form (if applicable) and Alliance Image Measurement Form (if applicable), must be submitted to the Imaging and Radiation Oncology Core (IROC). Images must be submitted from the following time points: baseline prior to initiation of radiation therapy, baseline after completion of radiation therapy and while on treatment. For patients who have progressive disease, submit one scan after confirmed progression and no further scans. For patients who go off study for reasons other than progression (i.e., toxicity) please continue to collect images until progression. **Institutions are permitted to batch ship images every six months. Sites must turn in images within 180 days of acquisition to be compliant with data submission.** BMP files, JPG files, or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the scan is accepted by the Imaging and Radiation Oncology Core. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number and protocol number. The de-identified digital images may be temporarily burned to a CD or transferred to a PC based system.

Data should be transferred electronically (**recommend**) to the IROC as follows:

Electronically

1) Web Transfer (http://upload.imagingcorelab.com**)**

Any PCs with internet access and web browser (e.g., Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to the Imagingand Radiation Oncology Core. The standard Web Transfer information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

2) FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of the Imaging and Radiation Oncology Core. The standard FTP access information will be provided separately through the specific trial e-mail, per the request by participating sites before their first data submission.

Mail/CD Shipment

Only if electronic data transfer approaches cannot be achieved, the de-identified images in digital DICOM format can be burned to a CD and mailed to the Imaging and Radiation Oncology Core. Submit only one patient's images per CD, with the patient's Alliance ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

Imaging and Radiation Oncology Core

Attn: Alliance Trial A071102

The Ohio State University

395 W. 12th Avenue, Suite 414

Columbus, Ohio, 43210

Tel: 614-293-9151

Fax: 614/293-9275

Once the imaging data submission is done, send an e-mail to the Imaging and Radiation Core at the specific trial email Alliance071102@irocohio.org to inform that the study has been submitted from the institution. Please include the basic information of submitted data sets as follows:

1) Alliance patient ID number
2) Scan time point (i.e., baseline)
3) Date of scans
4) Institution name

The Imaging and Radiation Core will acknowledge receipt of the imaging data via email confirmation to the institution within 1 business day of receipt, and will notify the institution and Alliance imaging committee of the quality check report within 3 business days.

6.6 Radiation Dosimetry Submission

SUBMISSION OF RADIATION DOSIMETRY TO THE IROC IS MANDATORY.

Isodose distributions must be submitted for the treatment plan. IMRT plans must be submitted electronically as DICOM RT Format to the IROC. 3D CRT plans should also be submitted electronically to IROC but may be submitted as screen captures if submission of digital RT data is not possible. Screen capture submissions should include at the least isodose distributions in the axial, sagittal and coronal planes through the center of the PTV, or if sagittal and coronal planes are not available, a minimum of at least five axial distributions (central axis, two superior,

and two inferior planes). Dose volume histograms for the targeted GTVs, PTVs, and Organs at Risk are required.

If you have questions about the digital data submission process, please contact the Imaging and Radiation Oncology Core at (614) 293-2929 or email **Alliance071102@irocohio.org**

7.0 Treatment Plan/Intervention

Protocol treatment is to begin ≤ 10 days of registration. For questions regarding treatment, please see the study contacts page.

It is acceptable for individual chemotherapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for Day 1 of a new cycle. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of chemotherapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

This is a randomized, double-blind trial. Blinded, patient-specific clinical supplies of veliparib/placebo will be requested by the Alliance Statistical and Data Center at the time of randomization and should arrive at the clinical site ≤ approximately 7-10 days of randomization (see Section 10).

Protocol therapy will consist of 6 cycles administered on days 1-7 of each 28 day cycle. Treatment will continue until disease progression (confirmed progression) or unacceptable adverse event or maximizing the dose reductions, for a maximum period of 6 cycles.

Agent	Dose	Route	Day	ReRx
temozolomide	150-200 mg/m^2	PO	Day 1-5	every 28 days
veliparib or placebo	40 mg bid	PO	Day 1-7	every 28 days

Patients will be treated with a combination of temozolomide and either veliparib or placebo. Temozolomide will be dosed at 150 mg/m2 PO once daily Days 1-5 for the first cycle of therapy. If this dose level is well tolerated (refer to Section 7.1.2 for details), then the dose of temozolomide should be increased in subsequent cycles to 200 mg/m2. If the dose is not escalated in cycle 2, then the dose of TMZ should remain at 150 mg/m2 for all 6 cycle. The dose of veliparib is fixed at 40 mg bid PO days 1-7 unless dose-reductions are required for toxicity. Because veliparib may accentuate the bone marrow suppression associated with temozolomide, pneumocystis pneumonia (PCP) prophylaxis is strongly recommended (see Section 8).

7.1 Adjuvant therapy with temozolomide and either veliparib or placebo

7.1.1 Patients will be treated with 6 cycles of oral temozolomide (days 1-5) and oral veliparib (twice daily on days 1-7). Cycles of treatment will be 28 days in length.

7.1.2 For cycle 1 of adjuvant therapy, temozolomide will be dosed at 150 mg/m^2/day. If no grade 3 or higher adverse events attributable to temozolomide occur in cycle 1, the dose of temozolomide should be escalated to 200 mg/m2/day for cycles 2 to 6. If the dose was not escalated at cycle 2, dose should not be escalated in subsequent cycles.

7.1.3 Temozolomide dosing should be based on actual body weight. The smallest temozolomide capsules are 5 mg. Therefore, patient doses of temozolomide will be rounded to the nearest interval of 5 mg. Temozolomide capsules should be taken with up to 200 mL of water on an empty stomach one hour before or two hours after food.

7.1.4 Veliparib should be administered at 40 mg/dose (irrespective of body weight) and should be taken twice a day (approximately 12 hours apart, irrespective of meals). If a dose is missed, it may be made up if taken within 4 hours of the scheduled dose (either morning or evening dose). If it is outside of this 4 hour window, the patient should not make up the missed dose of veliparib.

7.1.5 Patients with pseudoprogression can remain on study. See Section 11.4.3.2.

8.0 Dose and Treatment Modifications, Unblinding

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other anti-cancer agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 No other investigational therapy should be given to patients.

8.1.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as steroids, antidiarrheals, analgesics, antiemetics and/or antiepileptics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.4 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for serious medical condition or given in relationship to the disease as needed, and hormones administered for non-disease-related conditions (e.g., insulin for diabetes).

8.1.5 Antiemetics: Since temozolomide may cause nausea, an appropriate anti-emetic per institutional standard may be given in conjunction with temozolomide.

Additional symptoms should be managed as per standard antiemetic guidelines.

8.1.6 Diarrhea: This can be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and other antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics should be considered. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be evaluated and considered** for intravenous hydration and correction of electrolyte imbalances.

8.1.7 Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

8.1.8 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

Darbepoietin or Epoetin (EPO): Use of darbepoietin or epoetin in this protocol is NOT permitted in this protocol.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

Filgrastim/pegfilgrastim and sargramostim may not be used:

a. To avoid dose reductions or delays.

b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported.

c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.9 Palliative radiation therapy: Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.10 PCP Prophylaxis: Temozolomide with or without steroids can result in significant immunosuppression and places patients at increased risk for opportunistic infections such as Pneumocystis carinii pneumonia (PCP) and gram-negative organisms. Combined therapy with temozolomide and veliparib may increase this risk. Therefore, antibiotic prophylaxis is strongly recommended for patients treated on this protocol. Prophylaxis should start with the first day of cycle 1 (± 5 days) and should continue for at least 1 month following discontinuation of all drug therapy. The decision to continue PCP prophylaxis beyond this time point is left to the discretion of the treating physician. Patients who continue to demonstrate lymphopenia, 1 month after completion of the final cycle of TMZ therapy should be considered for ongoing prophylaxis.

Recommended prophylaxis regimens are listed below:

Trimethoprim/sulfamethoxazole (Bactrim): This is the preferred method. Initial therapy should be trimethoprim/sulfamethoxazole SS orally, 1 tablet daily; or trimethoprim/sulfamethoxazole DS orally 1 tablet, 3 times per week.

Dapsone may be given as 100 mg orally each day. Patients with prior history of G6PD deficiency are not appropriate candidates for dapsone and should be treated with an alternative regimen.

Pentamidine can be administered via inhalation (300 mg via aerosol) once per month.

Atovaquone may be administered at 1500 mg orally each day.

8.2 Dose Modifications

- The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.
- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- If the patient experiences a significant adverse event requiring a dose reduction at the start of the cycle, the dose will remain lowered for the entire subsequent cycle.
- Veliparib and temozolomide will not be re-escalated once reduced
- If dose reductions beyond lowest dose level is required OR either veliparib or temozolomide is held for 4 weeks, veliparib or temozolomide will be discontinued. If veliparib is discontinued, the patient may remain on temozolomide by itself to complete all 6 cycles. However, if temozolomide is discontinued, patient is off the treatment portion of the study.
- Please note that dose modifications do not apply to cycle 1. These are for cycle 2 forward.

CTEP-AERS reporting may be required for some adverse events (See Section 9.0).

8.2.1 Dose Levels

Dose Level	**veliparib/placebo** (Twice daily on Days 1 through 7	**Temozolomide Cycle 1 dose (dose reduction for cycle 2 on)**** (Daily on Days 1 through 5)	**Temozolomide Cycle 2-6 dose (dose reduction for cycle 3 on)** (Daily on Days 1 through 5)
0*	40 mg PO twice daily	150mg/m2/day	200mg/m2/day
-1	40 mg PO in AM, 20mg PO in PM	100mg/m2/day	150mg/m2/day
-2	20 mg PO twice daily	75 mg/m2/day	100mg/m2/day
-3	Discontinue	Discontinue	75mg/m2/day

*Dose level 0 refers to the starting dose.
**For patients who were unable to escalate to 200mg/m^2 at cycle 2, please use this column for any subsequent dose modifications

8.2.2 Hematological toxicity

- For **grade 2 neutrophil count decreased** on day 1, delay TMZ and veliparib until grade ≤ 1 then resume TMZ and veliparib at same dose. For **grade 2 neutrophil count decreased** on days 2-28, continue therapy with no change.
- For **grade 3 or 4 neutrophil count decreased** delay TMZ and veliparib until grade ≤ 1, then resume TMZ and veliparib at 1 dose level decreased.
- For **febrile neutropenia** at any time, delay TMZ and veliparib until resolved, then resume TMZ and veliparib at 1 dose level decreased.
- For **grade 2 platelet count decreased on day 1**, delay TMZ and veliparib until grade ≤ 1, then resume TMZ and veliparib at same dose. For **grade 2 platelet count decreased on days 2-28**, continue therapy with no change.
- For **grade 3 or 4 platelet count decreased**, delay TMZ and veliparib until grade ≤ 1, then resume TMZ and veliparib at one dose level decreased.

8.2.3 Gastrointestinal toxicity

- For **grade 3 nausea or grade 3 or 4 vomiting while on optimal antiemetic therapy,** delay TMZ and veliparib until grade ≤ 1, then resume TMZ and veliparib at 1 dose level decreased.
- For **grade 3 diarrhea,** delay TMZ and veliparib until grade ≤ 2, then resume TMZ at 1 dose level decreased and veliparib at same dose.
- For **grade 4 diarrhea,** delay TMZ and veliparib until grade ≤ 2, then resume TMZ and veliparib at 1 dose level decreased.

8.2.4 Neurotoxicity:

- For **grade 3 or 4 seizure in patients with seizures at pre-registration, and currently on optimal antiepileptic therapy,** delay veliparib until grade of seizures returns to baseline grade (grade at pre-registration), then resume veliparib at 1 dose level decreased.
- For **grade 3 or 4 seizure in patients with seizures at pre-registration, and currently not on optimal antiepileptic therapy,** delay veliparib until grade ≤ 1, then resume veliparib at 1 dose level decreased.
- For **grade 3 or 4 seizure in patients without prior incidence of seizures,** delay veliparib until grade ≤ 1, then resume veliparib at 1 dose level decreased.

8.2.5 Vascular disorders:

- For **grade 2 or 3 thromboembolic event,** delay TMZ and veliparib until medical intervention is initiated and patient deemed stable, then resume TMZ and veliparib at same dose.
- For **grade 4 thromboembolic event,** delay TMZ until patient deemed stable, then resume TMZ at same dose. Discontinue veliparib.

8.2.6 Other toxicity

- For other clinically significant **grade 3 or 4 non-hematologic toxicities** likely related to TMZ or veliparib, delay TMZ or veliparib. Resume drug at 1 dose level reduced when the toxicity resolves to grade 2 or less.

8.2.7 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined solely by actual weight without any modification. This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation. Physicians may consult the published guidelines of the American Society of Clinical Oncology Appropriate Chemotherapy Dosing for Obese Adult Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 30(13): 1553-1561, 2012.

8.3 Emergency Unblinding Procedures

Emergency unblinding will be available 24 hours a day, every day, according to the criteria below.

Unblinding can be done only in cases of an emergency. Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is unblinded, the patient must discontinue protocol therapy.

Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact the Alliance Executive Officer on call by calling 773-702-6800, pressing 1 to speak with an operator, and then asking for pager ID 8625 to return the call.

The institution must provide the following information to the Alliance Executive Officer:

- Study ID (A071102)
- Patient ID number
- Patient initials (e.g., "L, F, M")
- Institution name
- Name and telephone number of treating physician
- Name and contact information of person requesting the unblinding procedure
- Name and contact information of person to inform of treatment assignment
- Reason for unblinding request

Please remember that emergency unblinding request may be authorized only by an Alliance Executive Officer, and emergency unblinding applies only if unblinding would influence management of the medical situation.

After the Executive Officer deems unblinding is warranted, the treatment assignment will be provided to the contact person at the treating site.

9.0 Adverse Events

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at http://ctep.cancer.gov/ reporting/ctc.html. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

Please refer the **NCI Guidelines: Adverse Event Reporting Requirements** for further details on procedures to follow with AE reporting.

All Adverse Events are reported within RAVE, and are evaluated for seriousness by an automated process. All events deemed to be "reportable" in an expedited manner will be identified in by the RAVE application. Expedited reporting will use the CTEP-AERS systems as described below.

9.1 Routine adverse event reporting

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. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, RAVE is used for routine AE reporting.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Nausea	Gastrointestinal
Fatigue	General Disorders
Constipation	Gastrointestinal
Platelet Count decrease	Investigations
Anorexia	Metabolism and Nutrition Disorders
Neutrophil count decreased	Investigations
Diarrhea	Gastrointestinal
Headache	Nervous System Disorder
Seizures	Nervous System Disorder

9.2 CTCAE Routine Study Reporting Requirements

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a. Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b. Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 CTEP Adverse Event Reporting System (CTEP-AERS)

This trial has been selected to participate in the pilot of the caAERS/RAVE integration. Every reported adverse event will be required to be submitted for rules-validation in RAVE. After submission, a recommendation will be provided in terms of the need for expedited reporting and the timeframe for submission. All AEs requiring expedited reporting will be submitted via CTEP-AERS.

Investigators are required by Federal Regulations to report serious adverse events as defined in below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting. All expedited reports will occur through the CTEP Adverse Event Reporting System (CTEP-AERS). This system can be accessed via the CTEP home page, http://ctep.cancer.gov. In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for reporting. All treatment areas should have access to a copy of the CTCAE. It can be downloaded from CTEP website (http://ctep.cancer.gov).

The Alliance requires investigators to route all expedited adverse event reports through the Alliance Central Protocol Operations Program Office for Alliance – coordinated studies.

Be sure to read this entire protocol section, as requirements are described in both table and bullet points following the table. In case of a conflict between the table and the bullet points, the bullet points (additional instructions or exclusions) supersede the table.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND ≤ 30 Days of the Last Treatment [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last treatment require reporting as follows:

Expedited 24-hour notification followed by complete report ≤ 5 calendar days for:

- All Grade 4, and Grade 5 AEs that are at least possibly related to treatment

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization, and that are at least possibly related to treatment
- Grade 3 adverse events that are at least possibly related to treatment

Additional Instructions or Exclusion to CTEP-AERS Adverse Event Reporting System for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB, according to local IRB policies.
- Alliance A071102 uses a drug under a CTEP IND. These reporting requirements should be followed for all agents (any arm) in this trial.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results.
- Deaths clearly due to progressive disease do not require CTEP-AERS, but must be reported as part of the study results via routine reporting.
- Treatment expected adverse events include those listed in Section 10.0, in the package insert for temozolomide, in the CAEPR and the IB for ABT-888. The SPEER column of the ABT-888 CAEPR includes "expected" severity grades in addition to event terms.
- **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.

  CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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 each protocol.

  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.

- All pregnancies and suspected pregnancies occurring in female patients or in the partner of a male patient during therapy or within 28 days after completion of treatment on A071102 must be reporting via CTEP-AERS. In CTCAE version 4.0, use the event term, *"pregnancy, puerperium, and perinatal condition-other, fetal exposure (grade 4)"*.
  - CTEP-AERS reports should be amended upon completion of the pregnancy to report pregnancy outcome (e.g. normal, spontaneous abortion, therapeutic abortion, fetal death, congenital abnormalities).
  - The CTEP-AERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth independent of attribution. Infant deaths occurring after 28 days considered to be related to in utero exposure to the agents used in this trial should be reported via CTEP AERS.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g. cooperative group data reporting.

9.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for ABT-888 (Veliparib, NSC 737664)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 565 patients.* Below is the CAEPR for ABT-888 (veliparib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, March 22, 2013[1]

Adverse Events with Possible Relationship to for ABT-888 (Veliparib) (CTCAE 4.0 Term) [n= 565]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***

	Headache		***Headache (Gr 2)***
		Seizure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
		Thromboembolic event[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Thromboembolic events, including deep vein thrombosis and pulmonary embolism, have been observed at a higher frequency compared to control arm when administered in combination with temozolomide.

Also reported on ABT-888 (veliparib) trials but with the relationship to ABT-888 (veliparib) still undetermined:

CARDIAC DISORDERS - Left ventricular systolic dysfunction
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Dry mouth; Dyspepsia; Dysphagia; Enterocolitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (mouth ulceration); Lower gastrointestinal hemorrhage; Mucositis oral; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Fever; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Lymph gland infection; Skin infection; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hypernatremia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Pain in extremity
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Lethargy; Paresthesia; Peripheral sensory neuropathy; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura
VASCULAR DISORDERS - Hot flashes; Hypotension; Vascular disorders - Other (brainstem infarction)

Note: ABT-888 (veliparib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 Drug Information

10.1 General Considerations:

- Temozolomide dosing will be based on actual body weight. The smallest temozolomide capsules are 5 mg. Therefore, patient doses of temozolomide will be rounded to the nearest interval of 5 mg.
- It is not necessary to change the doses of temozolomide due to changes in weight unless the calculated dose changes by ≥10%.

10.2 Temozolomide for Oral Administration (Temodar®, TMZ)

PROCUREMENT

Commercial supplies.

FORMULATION

Commercially available for oral administration as: Capsules: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg

PREPARATION, STORAGE AND STABILITY

Refer to package insert for complete dispensing instructions. Store capsules at room temperature of 15ºC to 30ºC.

ADMINISTRATION

Refer to the treatment section for specific administration instructions. Capsules should not be opened or chewed but swallowed whole with a glass of water. Temozolomide may be administered on an empty stomach to reduce nausea and vomiting. Bedtime administration may be advised. Do not repeat if vomiting occurs after dose is administered, wait until the next scheduled dose.

DRUG INTERACTIONS

Ethanol/Nutrition/Herb Interactions: Food reduces rate and extent of absorption.

PHARMACOKINETICS

Absorption: Rapid and complete

Distribution: V_d: Parent drug: 0.4 L/kg; penetrates blood brain barrier; CSF levels are ~35% to 39% of plasma levels

Protein binding: 15%

Bioavailability: 100%

Time to peak, serum: Empty stomach: 1 hour; with food (high-fat meal): 2.25 hours

Metabolism: Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO_2 and 5-aminoimidazole-4-carboxamide (AID), a natural constituent of urine

Half-life elimination: Mean: Parent drug: 1.8 hours

Excretion: Urine (~38%; parent drug 6%); feces <1%

Clearance: 1.45 L/hour

ADVERSE EVENTS

Consult the package insert for the most current and complete information. With CNS malignancies, it is difficult to distinguish between CNS adverse events caused by temozolomide versus the effects of progressive disease.

Common known potential toxicities, > 10%:

Cardiovascular: Peripheral edema (11%)

Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)

Dermatologic: Alopecia (55%), rash (8% to 13%)

Gastrointestinal: Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)

Hematologic: Lymphopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%), neutropenia (grades 3/4: adults: 8% to 14%), leukopenia (grades 3/4: 11%)

Miscellaneous: Viral infection (11%)

Less common known potential toxicities, 1% - 10%:

Central nervous system: Amnesia (10%), insomnia (4% to 10%), somnolence (9%), ataxia (8%), paresis (8%), anxiety (7%), memory impairment (7%), depression (6%), confusion (5%)

Dermatologic: Pruritus (5% to 8%), dry skin (5%), radiation injury (2% maintenance phase after radiotherapy), erythema (1%)

Endocrine & metabolic: Hypercorticism (8%), breast pain (females 6%)

Gastrointestinal: Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), taste perversion (5%), weight gain (5%)

Genitourinary: Incontinence 98%), urinary tract infection (8%), urinary frequency (6%)

Hematologic: Anemia (grades 3/4: 4%)

Neuromuscular & skeletal: Paresthesia (9%), back pain (8%), abnormal gait (6%), arthralgia (6%), myalgia (5%)

Ocular: Blurred vision (5% to 8%), diplopia (5%), vision abnormality (visual deficit/vision changes 5%)

Respiratory: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)

Miscellaneous: Allergic reaction (up to 3%)

Rare toxicities <1%:

Alkaline phosphatase increased, alveolitis, anaphylaxis, aplastic anemia, emotional lability, erythema multiforme, febrile neutropenia, flu-like syndrome, hallucination, hematoma, hemorrhage, herpes simplex, herpes zoster, hyperglycemia, hypokalemia, interstitial pneumonia/pneumonitis, myelodysplastic syndrome, opportunistic infection (e.g., PCP), oral candidiasis, pancytopenia, peripheral neuropathy, petechiae, pneumonitis, pulmonary fibrosis, secondary malignancies (including myeloid leukemia), Stevens-Johnson syndrome, toxic

epidermal necrolysis and liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

NURSING GUIDELINES

- Myelosuppression has been found to be the dose-limiting toxicity. Gr 3 thrombocytopenia occurred in 6% of patients and Gr 4 in 1%. Gr 3 and Gr 4 lymphopenia occurred in 55% of patients. Leukopenia, lymphopenia, thrombocytopenia and anemia usually occur 2-8 weeks after initiation of treatment. Monitor CBC carefully and report any significant changes to MD. Instruct patient to report signs/symptoms of infection, unusual bruising and bleeding to health care team.

- In previous studies, patients have developed pneumocystis carinii pneumonia (PCP) when taking concomitant temozolomide and steroids. Instruct patient to report any fever, cough, chest pain, of other signs of infection to the health care team. Counsel patients on the importance of taking PCP prophylaxis as prescribed if ordered.

- Advise patient that a mild-moderate rash may be experienced.

- Fatigue may be experienced. Work with patient in energy conserving lifestyle.

- Remind patient that drug needs to be taken on an empty stomach with a full glass of water. Drug should not be crushed, chewed, opened, or dissolved.

- Nausea and vomiting are common. Teach patient to self-medicate with anti-emetics as directed by their healthcare provider. Assess for effectiveness. If vomiting occurs, do not repeat dose. Wait until next scheduled dose.

- Constipation can occur. Encourage patient to increase fluid intake. Administer stool softeners or laxatives if ordered and monitor for their effectiveness.

- Headache may be seen. Assess for more serious condition (i.e. cerebral bleed, disease progression) first and then treat symptomatically and monitor for effectiveness.

10.3 Veliparib or Placebo (NSC 737664, ABT-888, IND# 122646)

a. Description

Chemical Name: 2-[(R)-2-methylpyrrolidin-2-yl]-1H-benzimidazole-4-carboxamide

Other Names: A-861695.0, ABT-888

Classification: Poly (ADP-ribosome) polymerase (PARP) Inhibitor

Molecular Formula: $C_{13}H_{16}N_4O$

Molecular Weight: 244.29

Description: light orange opaque capsule with two black bands

b. PHARMACOLOGY

Storage: Store intact bottles between 15° and 25°C (59° – 77°F).

Stability: Shelf-life stability studies for veliparib/placebo capsules are ongoing.

Route(s) of Administration: Oral. Veliparib and matching placebo capsules may be administered without regard to meals.

c. SUPPLIER

Clinical Supplies: Veliparib (NSC 737664/ IND 122646) and matching Placebo will be provided free of charge by AbbVie Inc. and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Veliparib 20 mg and 0 mg matching placebo will be supplied as immediate release capsules. The veliparib capsule contains veliparib, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5. The matching placebo capsule contains microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide. May contain FD&C blue #1, FD&C yellow #6, or FD&C yellow #5.

Veliparib and matching Placebo will be supplied in bottles containing 64 capsules with a child-resistant cap and a tamper-evident seal.

Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., “A071102”)
- the bottle number (i.e., “Bottle 1 of 1”
- the number of capsules (i.e., “64 capsules”)
- the patient ID number (e.g.,"XXXXXXXXX", which represents the unique patient identifier assigned at registration)
- the patient initials (i.e., Last initial, First initial, Middle initial [e.g., "LFM"])
- the agent identification (i.e., “Veliparib 20 mg or Placebo”
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take __ capsules two times daily for 7 days as directed.”)
- storage instructions (i.e., “Store at room temperature (15ºC to 25ºC; 59ºF to 77ºF).”
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2014 = 14, 2015 = 15) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2014 would have a Julian date of ‘14001’ and a bottle labeled and shipped on December 31, 2014 would have a Julian date of ‘14365’. The Julian date will be used by PMB for recalls. When a lot

expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both veliparib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (240) 276-6575 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact the PMB via e-mail at PMBAfterHours@mail.nih.gov.

Agent Orders:
No blinded starter supplies will be available for this study. Blinded, patient specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within approximately 7 to 10 days. This randomization will be performed by the Alliance Statistical Center. The assigned Alliance patient ID number must be recorded by the registering institution for proper bottle dispersion. Once a patient has been registered, the Alliance Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the Alliance Statistical Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by FedEx Ground (up to 5 business days for delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). Shipments to United States sites can be expedited by the provision of an express courier account name and number to the Alliance Statistical Center at the time the patient is randomized. Please note that additional processing time is required for QA/QC checks on patient-specific/blinded orders and next day delivery is not available.

The initial request will be for 1 bottle [a 2 cycle (8 week) supply] of 20 mg capsules of veliparib or matching placebo at the recommended starting dose of 40 mg BID for 7 days of a 28 day cycle. After 6 weeks (two weeks before needed), sites may reorder an additional 1 bottle [a 2 cycle (8 week)] supply using the PMB On-line Agent Order Processing (OAOP) program. The assigned patient ID number (e.g., "XXXXXXX") and the patient initials (e.g., "LFM") should be entered in the "Patient or Special Code" field. A separate order is required for each patient ID number (e.g., "XXXXXXX") being ordered. All drug orders should be shipped directly to the physician responsible for treating the patient.

Agent Transfers: Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "XXXXXXX"') and the patient initials (e.g., "LFM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "A071102").

Agent Returns: Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "XXXXXXX") and the patient initials (e.g., "LFM") should be entered in the "Lot Number" field. Opened bottles with remaining capsules should be documented on the patient-specific Oral NCI Investigational Agent Accountability Record (i.e., logged in as “returned by

patient" and logged out as "destroyed on site") and destroyed on-site in accordance with institutional policy.

Agent Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Oral NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate Oral NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "XXXXXXX") on this protocol.

ADMINISTRATION

Administer veliparib orally without regard to meals.

DISPOSAL

Patients should return drug on day 1 of each cycle for cycle 2 and beyond. Drug destruction is per institutional standard.

DRUG INTERACTIONS

Clinical studies evaluating the metabolism of veliparib have not been conducted. However, results from the in vitro analysis reveal that his agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19, and 3A4. Veliparib is neither a potent inhibitor nor a potent inducer of the CYP450 isoenzymes. Use caution when concomitantly administering medications that are substrates, inhibitors, or inducers of CYP1A1, 2D6, 2C19 and 3A4.

Veliparib clears primarily in the urine as intact parent drug along with metabolites suggesting that renal function plays an important role in the drug clearance and its metabolites. Use caution when concomitantly administer with oxaliplatin, carboplatin, cisplatin, and topotecan in patients with pre-existing renal impairment.

PHARMACOKINETICS

Absorption: The absorption of veliparib after oral dosing was relatively rapid, with average time to maximum observed plasma concentration (Tmax) ranging from 1 to 2 hours across dose levels. The maximum observed plasma concentration (Cmax) and the area under the plasma concentration curve from time zero to infinity (AUC∞) of veliparib were approximately dose-proportional across the dose range studied, with minimal accumulation following BID dosing. Available data, while not definitive, shows an absence of significant food effect.

Distribution: The apparent volume of distribution (V/D) of veliparib was large, and oral clearance was rapid.

Metabolism: Results from in vitro analysis reveal that this agent is metabolized by multiple isoenzymes – CYP1A1, 2D6, 2C19 and 3A4. Veliparib has one major metabolite in plasma, M8, a lactam derivative of the parent drug. The cellular PARP-inhibitory activity of M8 is 18-fold lower than veliparib.

Excretion: The average terminal half-life (t½) of veliparib ranged from 4 to 5 hours across dose levels. Recovery of the dose as parent drug in the urine over 24 hours after dosing averaged 78% (N = 6). Following multiple oral doses given twice daily, total recovery of the dose in the urine (as both parent drug and M8 metabolite) over 12 hours averaged 86% (N = 34). Veliparib is primarily cleared in the urine as intact parent drug along with metabolites, suggesting that renal function plays an important role in the clearance of veliparib and its metabolites. Coadministration of veliparib with oxaliplatin, carboplatin, cisplatin, and topotecan should be

used with caution in patients with pre-existing renal impairment since the primary elimination route of all of these drugs is renal.

ADVERSE EVENTS
Refer to the CAEPR.

NURSING GUIDELINES:

- Cytopenias are common. Monitor CBC and instruct patients to report any signs or symptoms of infection, bruising or bleeding to the study team.
- Gastrointestinal side effects (nausea, vomiting, and diarrhea) have been seen. Treat symptomatically and monitor for effectiveness.
- Patients may experience loss of appetite and subsequent weight loss. Instruct patients to eat frequent small meals and monitor their weight.
- Maculo-papular rash can occur. Sun exposure may exacerbate this rash. Instruct patient to avoid prolonged sun exposure and to report any rash to the study team.
- Fatigue is common. Patients should be taught about an energy conserving lifestyle.

11.0 Measurement of Effect

Tumor response and regrowth can frequently be difficult to measure directly. Serial MRI/CT scans along with neurological exams will provide a guide for the effectiveness of therapy and the time-course of the disease. **It is important to note that this particular study is likely to result in a higher than normal incidence of treatment-related contrast enhancement, or "pseudoprogression," due to the nature of the tumor phenotype (i.e. MGMT promoter hypermethylation) and the treatments involved.**

Time interval to progression will be measured from registration until deterioration is documented by the individual investigator using the guidelines in Section 11.4. The patient should use the same diagnostic imaging modality (MRI or CT) throughout the study. Ideally, patients should also be evaluated on the same physical imaging device throughout the length of the study to ensure the most accurate assessments of tumor response. (Note: The CT evaluation option should ONLY be used for patients unable to undergo MR imaging because of non-compatible devices).

Overall survival will be measured from registration to death. Progression-free survival will be measured from registration until the first occurrence of progression or death. The quality of survival will be measured by performance status.

The primary measure of response will be by serial measures of the product of the two largest cross-sectional diameters (bidirectional product) using the RANO criteria (59).

Acquisition of MR imaging in a uniform manner for all patients across the study and for an individual patient on serial imaging, we have defined the standard imaging parameters that are required for imaging on 1.5 T and 3 T MRI scanners (Appendix II). Institutions should use these imaging parameters for all imaging sessions for all patients enrolled on this trial.

A secondary objective of this study is to evaluate whether advanced MR imaging can be used to more clearly differentiate pseudoprogression from true progression. Therefore, we have also defined a set of imaging parameters and contrast administration for dynamic susceptibility contrast (DSC) and diffusion weighted imaging (DWI) (Appendix III). Recognizing that not all institutions can perform

this advance MR imaging readily, institutions may elect to participate or to not participate in the advanced MR imaging portion of this study. For those institutions that elect not to participate in this portion of the study, the patients should not be registered to the imaging sub-study.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 8 weeks while on therapy and then at a minimum every 3 months for years 1-3 and every 6 months for years 4 and 5 after completion of therapy, or until confirmed progression.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

We will define Measurable and Non-Measurable disease according to the updated RANO criteria (59). In short, measurable disease requires bidimensional contrast enhancing lesions with clearly defined margins on MRI (or CT scan) with two perpendicular diameters of at least 10mm, visible on two or more axial slices that are at most 5 mm in thickness (0-mm skip).

11.2.2 Non-Measurable Disease

We will define non-measurable disease as either unidimensionally measurable lesions, masses with indistinct margins, or lesions with maximal perpendicular diameters less than 10mm.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. We will measure all lesions in millimeters using standard ruler tools in the PACS system.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional MRI and CT:** CT scan imaging is only acceptable if patients are medically unable to undergo MR evaluation. This guideline has defined measurability of lesions on MRI scan based on the assumption that MRI slice thickness is 5 mm or less. If MRI scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with MRI, if a CT scan is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the brain tumors. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5 lesions, should be identified as “Target Lesions” and recorded and measured at baseline.

Note: If fewer than 5 target lesions are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions should be selected on the basis of their size, be representative of all involved sites of disease, and should lend themselves to reproducible and repeated measurements.
- **Baseline Sum of Largest Bi-Dimensional Measurement (Baseline BDM):** The sum of product of the largest bi-dimensional measurements for all target lesions will be calculated and reported as the baseline sum of bi-dimensional measurement. The baseline sum of the largest bi-dimensional measurement will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of Bi-Dimensional Measurement (Post-Baseline BDM):** The sum of product of the largest bi-dimensional measurements for all target lesions will be calculated and reported as the post-baseline sum of bi-dimensional measurements (Post-Baseline BDM). If the radiologist is able to provide an actual measure on the target lesion, that should be recorded. If the target lesion is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm^2 should be assigned. If it is the opinion of the radiologist that the target lesion has likely disappeared, the measurement should be recorded as 0 cm^2.
- The minimum sum of the largest bi-directional measurements (Minimum BDM) is the minimum of the BDM of the baseline and post-baseline BDMs.

11.4.2 Non-Target Lesions

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions and should also be recorded at baseline.

11.4.3 Response Criteria

11.4.3.1 Radiographic response should be determined in comparison to the tumor measurements obtained at pre-treatment baseline (post-radiation scan obtained prior to trial registration) for determination of response, and the smallest tumor measurement at either pre-treatment baseline or following initiation of therapy for determining progression.

Because the current treatment is likely to result in a higher than normal incidence of treatment-related contrast enhancement ("pseudoprogression"), patients should continue therapy with close observation (e.g. 4 to 8 week intervals) if there is a suspicion of pseudoprogression. If subsequent imaging studies and/or clinical observations demonstrate that progression in fact has occurred, the date of confirmed progression should be noted as the scan at which the potential progression was first identified. We will define complete response, partial response, progressive disease, and stable disease based on updated RANO criteria (59). We will consider all measurable disease as target lesions.

11.4.3.2 Evaluation of Target Lesions

- **Pseudoprogression (PsP):** All of the following must be true:
  a. Progression of contrast enhancing lesions and or T2/FLAIR is restricted to the initial radiation therapy volume.

b. There are no new enhancing lesions outside of the initial radiation therapy volume.
c. Patients are stable or improved clinically.
d. PsP may be diagnosed at any time during therapy (beyond the typical 12 week window defined by RANO).

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all enhancing measurable and non-measurable disease (sustained for at least 4 weeks).
  b. No new enhancing lesions.
  c. Stable or improved non-enhancing (T2/FLAIR) lesions
  d. Patients must be off corticosteroids (or on physiologic replacement doses only).
  e. Stable or improved clinically

NOTE: Patients with non-measurable disease only cannot have CR; the best response possible is stable disease.

- **Partial Response (PR):** Requires all of the following:
  a. $\geq$ 50% decrease in sum of products of perpendicular diameters of all measurable enhancing lesions (sustained for at least 4 weeks) compared with baseline.
  b. No progression of non-measurable disease
  c. No new lesions
  d. Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
  e. Steroid dose should be same or lower compared with baseline scan.
  f. Stable or improved clinically

NOTE: Patients with non-measurable disease only cannot have PR; the best response possible is stable disease.

- **Progression (PD):** Defined by any of the following:
  a. $\geq$ 25% increase in sum of products of perpendicular diameters of enhancing lesions, compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response (on stable or increasing steroid dose).
  b. Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after therapy initiation (stable doses of steroids include patient not on steroids) not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative change).
  c. Any new lesion
  d. Clear clinical deterioration not attributable to other causes apart from tumor (e.g., seizures, medication adverse effect, therapy complication, stroke, infection) or change in corticosteroid dose
  e. Failure to return for evaluation as a result of death or deteriorating condition
  f. Clear progression of nonmeasurable disease

- **Stable Disease (SD):** Requires all of the following:
  a. Does not qualify for complete response, partial response, or progression.
  b. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.
  c. In the event that corticosteroid dose was increased (for new symptoms/signs) without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that the steroid increase 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.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, and new disease as defined in the following tables:

NOTE: Patients with possible PsP should initially be given the Objective Status of Preliminary Progression. Once PsP or Progression is confirmed, the Objective Status can be changed accordingly.

For Patients with Measurable Disease

Target Lesions	New Sites of Disease	Overall Objective Status
CR	No	CR
PR	No	PR
SD	No	SD
Not all Evaluated	No	Not Evaluated (NE)
PD	Yes or No	Confirmed PD
CR/PR/SD/PD/Not all Evaluated	Yes	Confirmed PD
Possible PsP		Preliminary PD
PsP	No	PsP

11.4.5 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 End of Treatment/Intervention

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy for a total of 6 cycles. Patients with possible pseudoprogression (preliminiary progression) also should remain on therapy. After treatment is discontinued, patients will be followed per the study calendar in Section 5.0.

12.1.2 Disease Progression:

Patients who develop PD while receiving therapy will go to the survival and disease follow up phase.

True progression versus pseudoprogression: Given the high incidence of pseudoprogression (20-30% of patients) following standard radiotherapy with concurrent/adjuvant temozolomide, the development of enhancement following therapy cannot be assumed to represent tumor progression. Differentiation between true progression and post-treatment effects (i.e., pseudoprogression, radiation necrosis) is difficult based on conventional MRI alone, as these entities appear identically with contrast enhancement, mass effect, and abnormal T2/FLAIR signal. The updated RANO criteria have attempted to address this issue (59). In short, tumor progression can only be determined within the first 12 weeks of completing chemo-radiation therapy if the majority of the enhancement is outside of the radiation field (80% isodose line) or if radiographic changes within the radiation field are associated with clinical deterioration, requirement for escalating steroid doses, or pathologic confirmation of tumor progression; otherwise, the diagnosis of pseudoprogression should be made. There may be a higher than normal rate of pseudoprogression on this study, and pseudoprogression may occur later than normally observed when using a TMZ-sensitizing strategy. Moreover, the 'intensity' of pseudo-progression in a given patient may be higher for individual patients. Therefore, for this trial, pseudoprogression may be defined at any time during treatment on this study and stable steroid doses are not required to make a presumed diagnosis of pseudo-progression as long as patients remain clinically stable. Patients with probable pseudoprogression should continue on therapy until true progression is confirmed or they complete adjuvant therapy.

12.1.3 Discontinuation of study agent: Patients who go off protocol treatment for reasons other than PD will go to post treatment follow up, then to the survival and disease status follow up per Section 5.0. Patients that refuse post treatment follow up will also go to survival and disease status follow up phase.

12.2 Managing ineligible and canceled patients and major protocol violations

Data must be submitted per Section 5.0 for patients deemed ineligible or canceled. See also the Forms Packet for full details of data submission requirements. If a patient is deemed ineligible, they may be replaced.

12.2.1 Definitions

Cancelled Patient: A study participant who is registered to the trial but never receives study treatment.

Ineligible Patient: A study participant who is registered to the trial but does not meet all of the eligibility criteria at time of registration.

Clinical Follow-up: The follow-up period where the study participant is no longer receiving treatment, but is still following the study calendar for tests, exams, and

correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study).

Survival Only Follow-up: The follow-up period where the study participant is monitored for long-term endpoints, is no longer receiving study treatment, and is not required to follow the study calendar for tests, exams, and correlative endpoints (e.g., specimen collection, quality of life, disease assessments as required by the study). In this follow-up period, there is a schedule in which case report forms should be submitted, but the physician visits are based on the standard of care.

12.2.2 Follow-up Requirements

Patients who are deemed ineligible may continue protocol treatment provided the treating physician, study chair, and Executive Officer agree there are no safety concerns. If the patient continues protocol treatment, all scans, tests, data submission will continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 Statistical Considerations

13.1 Endpoints

13.1.1 Primary Endpoint

The primary endpoint is overall survival, which is defined as the date from study registration to the date of death due to any cause. A dynamic allocation procedure with a 1:1 randomization will be used to allocate an equal number of patients to two arms. This procedure will balance the marginal distributions of the stratification factors among arms. The stratification factors that will be used are: age (≤ 70 vs. >70), performance score (ECOG 0-1 vs. 2), and extent of resection (gross total resection vs. subtotal resection or biopsy).

13.1.2 Secondary Endpoints

- **Progression-free survival**: is defined as the date from study registration to the date of first observation of disease progression or death due to any cause (whichever comes first).
- **Objective tumor response**: is defined as CR or PR as specified in the RANO criteria in Section 11. Pseudoprogression is defined in Section 11.4.3.2.
- **Treatment-related Adverse Events**: As per CTEP Active Version of the CTCAE, the phrase "treatment-related adverse event" is defined as an adverse event that is classified as either "possibly," "probably," or "definitely related" to study treatment.

13.2 Sample Size Derivation

The phase III portion of the study has OS as an endpoint with one interim analysis (to be done after the completion of the Phase II portion). Based on the RTOG 0525 study, the median overall survival (OS) for patients with MGMT promoter methylation assessed by the standard qMS-PCR assay planned in this study is about 21.2 months with standard therapy of RT/TMZ followed by adjuvant TMZ. In the phase II portion of the study, we plan to enroll a total of 293

patients (73% of total patients needed for phase III comparison) in 4.1 years (49 months), and then hold the accrual for 6 months to get a total of 160 death events (53% of events needed for phase III comparison), at which time we will perform an interim analysis (to be done by an independent statistician). When 160 deaths have been observed, about 4.6 years after study opening (4.1 years for accrual and 0.5 years for follow up), we will compare the OS curves and resume the accrual and move on to phase III portion only if the observed OS HR is 0.875 or smaller (an observed increase in median OS from 21.2 to 24.2 months). Once the study moves on to the phase III portion, we plan to accrue another 107 patients (for a total sample size of 293+107=400 in phase III) in 1.5 years (18 months) with a minimum follow up of 2 years to get a total of 302 death events. This design with one interim analysis for futility will yield 90% power to detect a hazard ratio of 0.71 (median OS of 21.2 vs. 29.7 months) using a one-sided log-rank test with a type I error rate of 0.05. The final analysis of the phase III trial will occur when 302 deaths have been observed (expected to be approximately 3.5 years after phase III portion opens) and we will conclude the combination therapy TMZ/ABT888 extends the OS significantly if the observed OS HR is 0.82 or smaller (an observed increase in median OS from 21.2 to 25.6 months).

13.3 Analysis plans

13.3.1 Phase II Analysis

The phase II trial has PFS as the primary endpoint and will have one interim analysis for futility (accrual will not stop for this interim analysis) using a Lan-DeMets boundary. A total sample size of 293 for the phase II trial will yield 90% power to detect a HR of 0.67 (equivalent to the median PFS of 8.7 vs. 13.0 months) using a one-sided log-rank test with a type I error rate of 0.2 and one interim analysis for futility. The interim analysis for the phase II will occur after 79 PFS events have been observed. We will recommend the trial be stopped for futility if the observed HR (comparing control to experimental arm) is greater than 0.97 at the interim analysis. At the end of the phase II trial we will perform an analysis when 121 PFS events have been observed. We will recommend not proceeding with the phase III trial if the observed HR is 0.86 or greater.

13.3.2 OS Interim Analysis at End of Phase II

Accrual will be suspended at the end of the phase II portion of the trial (once 293 patients have been accrued) until 160 deaths have been observed. At this point, an independent statistician (one not associated with this trial) will perform an interim analysis of the OS data. The independent statistician will recommend that the trial be closed to accrual due to futility if the HR (comparing control to experimental) is greater than or equal to 0.875. This recommendation would imply that accrual to the phase III trial be halted. If HR for OS does not cross the futility boundary, the trial will be reopened to complete accrual for the Phase III portion. The independent statistician will not share the results of the OS analysis with the study team.

13.3.3 Analysis Plans for Primary, Secondary, and Exploratory Endpoints

- **Overall survival**: is defined as the date from study registration to death due to any cause. Efficacy analysis will be based on the intent-to-treat principle. The primary analysis of overall survival will occur after 302 deaths have been observed. The primary analysis will be a re-randomization test. To perform the test, 5000 simulations will be performed in which patients will be randomized according to the dynamic allocation procedures used in the original randomization. The order that the patients are entered into each simulated trial will be randomized. The p-value will be computed as the number of instances the simulated test-statistic (from

a stratified logrank test) is the same or more extreme than the observed test statistic from the trial data divided by 5000. Patients who are lost to follow-up will be censored at the date of their last follow-up. Patients still alive at the time of analysis will be censored. In addition as a secondary analysis, the distribution of OS for each arm will be estimated using the Kaplan-Meier method and compared with a stratified logrank test. . Stratified Cox proportional hazard models will be used to estimate the hazard ratio for the treatment effect

- **Progression Free Survival**: The distribution of PFS for each arm will be estimated using the Kaplan-Meier method, and be compared using Cox proportional hazard models with all stratification factors adjusted.
- **Objective tumor response**: an objective tumor response will be evaluated for each patient and the tumor response rate will be summarized for each arm and compared using the Chi-square test.
- **Adverse Events**: The overall adverse event rates for grade 3 or higher adverse events will be summarized and be compared using Chi-Square or Fisher's Exact tests between treatment arms. The maximum grade for each type of treatment-related adverse event will be recorded for each patient, and frequency tables for each arm will be reviewed to determine patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either "unrelated" or "unlikely to be related" to study treatment in the event of an actual relationship developing. Adverse events and treatment-related adverse events will be evaluated using all patients who have received any study treatment as well as summarizing those who have been included in the efficacy analyses. Treatment-related adverse events will be tabulated for each arm.
- **Fatigue/Uniscale Assessment**: The fatigue/uniscale tool will be used as a measure of QOL for patients because fatigue has been identified as a particular concern for GBM patients. Potential differences in fatigue levels of patients treated on the two different arms will be evaluated. Changes in this measure will be evaluated over the course of treatment for both arms and will be compared using a two-sample t-test at each timepoint. We will also compute a normalized area under the curve (AUC) for the values of each patient over time and compare the mean AUCs for patients on the two arms. This aim is more exploratory than confirmatory. Results will be used to inform future trials.
- **Exploratory Endpoints**: Binary or categorical exploratory endpoints will be compared using Chi-Square or Fisher's Exact tests between treatment arms, and continuous exploratory endpoints will be analyzed using change-from-baseline measures and compared using t-tests between treatment arms.
- The concordance between site-determined MGMT methylation status and central laboratory determination of MGMT status will be analyzed using the Chi-Square test of proportions and 95% confidence intervals for the proportion of tests in disagreement with the local site.

13.3.4 Accrual and Study Duration

The study will be opened to all sites within The Alliance for Clinical Trials in Oncology (the Alliance) and to other cooperative groups through the CTSU mechanism. All patients enrolled must have tumor MGMT hypermethylation determined by the study central laboratory. We anticipate 338 GBM patients per year will be registered for pathology central review and central MGMT testing. In the RTOG 0525 experience, 71% of patients registered for screening were ultimately randomized to therapy, and 30% of patients with MGMT testing were found to have MGMT promoter hypermethylation. Thus, we expect the accrual

rate will be about 72 evaluable methylated (338*71%*30%) patients per year from screening.

A minimum of 208 and a maximum of 322 eligible patients, including an extra 10% each to accommodate losses due to cancellations, ineligibility, or major protocol violations, will be entered into the phase II trial. Similarly, a maximum 118 eligible patients will be entered into the phase III. The study duration will be a minimum of 2.7 years (32 months) and a maximum of 4.6 years for the phase II, and an additional 3.5 years for the phase III portion. Therefore, the entire study may take between 2.7 years and 8.1 years. Based on the assumptions described above, the Phase II portion of the trial will require a maximum of 1512 patients to be screened at the study central laboratory for MGMT methylation. For the Phase III portion of the trial, a maximum of 554 patients will be screened at the study central laboratory for MGMT methylation.

13.4 Monitoring the Study

13.4.1 Adverse Event Stopping Rule

For the experimental arm, if 3 out of the first 20 or if at any time after the first 20 patients are enrolled 15% or more patients on the experimental arm develop Grade 4 non-hematologic adverse events felt to be at least possibly related to treatment, the study team will review the data to determine the proper course of action. These actions may include further AE monitoring, suspension of accrual, dose modification, and closure of the trial. Accrual to the trial will continue until official notification is received from The Alliance. We will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event. CTCAE v4.0 will be used to determine grading.

13.4.2 Accrual Monitoring Stopping Rule

Accrual to the Phase-III portion of the study will be monitored closely. The study team will evaluate accrual within the 5th to 6th quarter from Phase-III activation. If accrual is less than 50% of what was projected, working together with the Alliance Data Safety Monitoring Board, we will plan modifications including the potential for closure.

13.5 Study Reporting

13.5.1 Alliance Data Safety Monitoring Board (DSMB)

Both the Phase-II and Phase-III portions of this study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, accrual, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.5.2 Clinical Data Update System (CDUS)

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. An abbreviated report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reporting time points are: January 31, April 30, July 31, and October 31.

13.6 Descriptive Factors

13.6.1 Location of Lesions

Frontal vs. temporal vs. parietal vs. occipital vs. crosses boundaries

13.6.2 Other Tumor Sites

Thalamus vs. basal ganglia vs. hypothalamus vs. brain stem vs. other.

13.6.3 Side of Lesion

Right vs. left vs. midline vs. bilateral.

13.6.4 Baseline Imaging Assessment – CT vs. MRI

13.6.5 Maximum Diameter

Maximal diameter in centimeters on a preoperative scan of:

1. Contrast enhancement.
2. Abnormal T_2 signal on MRI (specify) or low attenuation on CT.

13.6.6 Extent of Resection

Extent of resection (by treating physician's opinion): Biopsy vs. subtotal vs. gross total.

13.6.7 Family History of Brain Tumor

Yes vs. no.

If yes, check all that apply
_____Father
_____Mother
_____Brother or sister
_____Child
_____Other (list :_____)

13.6.8 Corticosteroid Therapy at Study Entry

Yes vs. no.

13.6.9 Anticonvulsant Use

Yes vs. no.

13.6.10 Radiation Therapy

RT Dose
60 Gy in 30 fractions vs. 59.4 Gy in 33 fractions

RT to T2 abnormality
Yes vs. no

Dose to T2 abnormality
<50 Gy vs. >=50 Gy

Number of fractions to treat T2 abnormality
<30 vs. >=30

CTV expansion of GTV T1 gad
<=1 cm vs. >1 cm

CTV expansion of GTV T2 abnormality
<=1 cm vs. >1 cm

PTV dose coverage, >= 95% Dose to >90% PTV
Yes vs. No

13.7 Inclusion of Women and Minorities

This study will be available to all eligible patients regardless of race, gender, or ethnic group.

There is no information currently available regarding differential agent effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for such subset analyses. A maximum of 1661 patients may be pre-registered to enroll a total of 440 eligible patients needed for the whole study.

Based on prior studies involving similar disease sites, we expect about 7% of patients will be classified as minorities by race and about 40% of patients to be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	12	19	31
Not Hispanic or Latino	164	245	409
Ethnic Category: Total of all subjects*	176	264	440
Racial Category			
American Indian or Alaskan Native	5	7	12
Asian	2	4	6
Black or African American	2	3	5
Native Hawaiian or other Pacific Islander	3	5	8
White	164	245	409
Racial Category: Total of all subjects*	176	264	440

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."
Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.
White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 Correlative and Companion Studies

The correlative science study **must be offered** to patients enrolled on A071102. There will be three sub-studies (A071102-ST1, A071102-ST2 and A071102-IM) and all patients are encouraged to participate.

14.1 DNA Extraction from Tissue (A071102-ST1)

14.1.1 Background

In the RTOG 0525 clinical study, qMS-PCR determination of MGMT promoter hypermethylation was observed in 30% of patients and associated with a median overall survival of 21 months as compared to 14 months for patients with hypomethylated (unmethylated) tumors. The qMS-PCR MGMT assessment was performed by Oncomethylome using a published methodology that is now commercially available by Lab Corp. An almost identical method is routinely used in both Dr. Sarkaria's and Dr. Sulman's laboratories, and in collaboration with Raja Luthra, Erik Sulman will perform this assay as a CLIA-certified test suitable for use in this clinical trial.

As part of a funded RO1, we are evaluating the efficacy of veliparib and TMZ in 18 primary GBM xenograft lines using our intracranial therapy evaluation model. These xenograft lines also will be characterized by aCGH, gene expression analysis, and exome sequencing to identify potential defects in various DNA repair processes involved in recovery from replication fork arrest that is induced by persistent O6MG lesions. Following this hypothesis generating exercise, molecular studies will be performed to validate potential mechanisms of sensitivity and or resistance to veliparib sensitizing effects in combination with TMZ. Based on these studies performed in our xenograft model, tumor samples accrued on the planned clinical trial as part of the MGMT analysis will be analyzed for these additional potential markers for response to combination therapy. Since the preliminary studies in our animal models are not complete, we are unable to define what these specific molecular tests will be at this time. Once these studies mature, then the clinical protocol will be amended to include specific analyses that are guided by these pre-clinical studies. However, in anticipation of these studies, we will collect a pre-treatment blood sample from each patient consenting to A071102-ST2 and archive normal genomic DNA for future studies.

14.1.2 Objectives

We would like to identify additional biomarkers that predict for response to the combination of veliparib and TMZ. Based on ongoing pre-clinical studies, we anticipate evaluating molecular alterations in DNA repair processes in exploratory studies that could be confirmed in subsequent clinical trials.

14.1.3 Methods

The specific nature of the future molecular studies focused on mechanisms of sensitivity to combination treatment with veliparib and TMZ have yet to be determined. This protocol section will be amended when the plan for these studies is finalized.

DNA will be extracted from patient tumor blocks as required for MGMT promoter methylation analysis. For most specimens, the amount of DNA extracted will be in excess of that required for MGMT methylation analysis. This unused DNA will be returned from Dr. Sulman's laboratory to the Alliance Biorepository at Mayo Clinic and will be archived for all patients who undergo screening for MGMT status.

We anticipate evaluating the mutation status in various DNA repair genes in the tumor DNA. Because there are rare germline single nucleotide polymorphisms in many of the DNA repair genes of potential interest, we will collect and isolate germline DNA from all patient that register for the therapeutic study. The DNA extraction will be performed by the Mayo Biospecimens Accessioning and Processing laboratory and then archived in the Alliance Biorepository at Mayo Clinic. Collection of this DNA is critically important to facilitate the planned analysis of somatic DNA repair gene mutations. Any future use of banked specimens will require review and approval according to the policies of the NCTN.

14.2 DNA Extraction from Blood (A071102-ST2)

14.2.1 Background

We hypothesize that subtle defects in DNA repair capacity may be important modulators of the TMZ-sensitizing effects of veliparib. This hypothesis currently is being studied in multiple pre-clinical animal models that were used to generate the preliminary data supporting this clinical trial. From initial RNAseq and whole exome-seq studies performed in our laboratory, we anticipate that single nucleotide variants (SNVs) or small insertion/deletion (INDEL) in the somatic tumor DNA can be linked to these defects in DNA repair associated with TMZ-sensitizing effects. Because any given tumor typically has numerous SNV or INDELs in the somatic DNA, a comparison of these sequence variants against germ-line DNA is an essential first step in determining whether a specific SNV or INDEL is functionally significant. Therefore, we will collect blood from all patients enrolled on this study and extract DNA from these samples to support the planned correlative studies directed at understanding somatic DNA variations associated with a sensitizing effect of veliparib.

14.2.2 Objectives

Isolate and archive germ-line DNA from all patients to support functional analysis of somatic mutations in tumor DNA.

14.2.3 Methods

DNA extraction from whole blood will be performed in the Biospecimen Accessioning and Processing (BAP) core laboratory at Mayo Clinic. Blood samples received in BAP will be processed to extract DNA using the AutoGenFlex STAR purification instrument along with the Qiagen FlexiGene DNA AGF3000 kit. The FlexiGene DNA AGF3000 kit is designed for automated purification of total DNA (i.e. genomic and mitochondrial DNA) from human whole blood using the AutoGenFlex STAR workstation. FlexiGene technology provides high-quality DNA that is free of protein, nucleases, and other contaminants or inhibitors. Typically, DNA extraction typically yields 100-150 ug of DNA. Once the DNA is extracted the sample will have its optical density (OD) measured to ensure the quality of the extraction. The sample then will be transferred to the Alliance Biorepository at Mayo Clinic

for archiving and storage. Any future use of banked specimens will require review and approval according to the policies of the NCTN.

14.3 Analysis of advanced MR imaging (A071102-IM)

14.3.1 Background

The Response Assessment in Neuro-Oncology (RANO) criteria have established criteria for assessing tumor progression vs. treatment effects by recommending that enhancing lesions on CE-MRI be followed over time to distinguish growing recurrent tumor from regressing post-treatment radiation effects (PTRE), including pseudoprogression (PsP) and radiation necrosis (59). Despite this recent advance in response criterion, driven by both awareness of PTRE/PsP and pseudoresponse in anti-angiogenic therapies, significant limitations remain. For example, comprehensive serial imaging generally delays both diagnosis and management by several months due to the time required to observe adequate tumoral or PTRE/PsP-related evolution. This results in clinical inefficiency that is compounded, in some cases, when PTRE/PsP continues to grow or remains stable. The requirement for serial imaging to ***retrospectively*** determine PTRE/PsP from tumor progression also adds significant costs to clinical trials. Additionally, CE-MRI poorly estimates the histologic admixture between tumor and PTRE/PsP, which almost universally follows standard multimodal therapies. Contrast enhancement alone can represent a combination of viable tumor, persisting PTRE/PsP, or a combination of both, making it difficult to diagnose the precise composition as well as changes in tumor behavior and kinetics. The relative quantity of tumor, as determined by histopathology, has been shown to correlate with both treatment response and OS, and offers more prognostic information than simply reporting the presence of tumor (60-64); however, surgical biopsies introduce additional medical risks, morbidities, and costs as well as limited information regarding the heterogeneity of tumor response. These issues highlight the critical need to improve the imaging-based clinical trial assessment of tumor progression.

Imaging for all patients enrolled on the study will be collected prospectively by the IROC. There are two purposes for this imaging banking. First, a secondary endpoint for this trial is progression free survival. Given the potential difficulties in differentiating tumor progression from PTRE/PsP, we plan to archive all images obtained during and immediately following therapy to facilitate future retrospective central radiology review of images. This is especially relevant since the rate of PTRE/PsP may be higher in MGMT methylated tumors and treatment with a TMZ-sensitizing agent may increase further the rate of PTRE/PsP. Thus, prospective collection and banking of images will ensure our ability to robustly address questions regarding differences in PTRE/PsP and time to tumor progression for each in the 2 treatment groups. Second, for institutions that elect to participate in the advanced MR imaging study, dynamic susceptibility contrast (DSC) and diffusion weighted imaging (DWI) will be performed at each imaging time point and submitted to the IROC along with the standard imaging studies. These advanced MR series will be analyzed as described below.

14.3.2 Objectives

- *Hypothesis #1*: Metrics on DSC will provide earlier and more accurate assessment of tumor progression (vs. PTRE/PsP) compared with RANO criteria assessment and will correlate more strongly with OS.

- *Hypothesis #2*: Probabilistic functional diffusion map (fDM) parameters will enable earlier and more accurate differentiation of PTRE/PsP from tumor progression compared with RANO criteria assessment.

- *Hypothesis #3*: Combining pMRI and ADC metrics will improve distinction of PTRE/PsP from tumor progression compared with traditional evaluations of tumor progression (i.e. RANO/Macdonald criteria).

14.3.3 Methods

Standardized dynamic susceptibility contrast (DSC) and diffusion weighted imaging (DWI) will be performed at each imaging time point as detailed in Appendix III. These advanced MR imaging series will be analyzed retrospectively using quantitative analyses to address 3 specific hypotheses listed above.

We expect approximately 60% of patients to participate in DSC-MRI and >80% of patients to participate in DW-MRI. Although these numbers are partially dependent on the imaging capabilities of the particular sites chosen for the study, we anticipate the majority of patients to have DW-MRI (as this is routinely used in clinical neuroimaging protocols) and fewer patients to have DSC-MRI because it is more technically challenging. As a reference, in ACRIN-6677 which did not have standardized DW-MRI acquisition protocols, 100% of patients had DW-MRI data collected, for which 68% of the DW-MRI data was usable. We expect this percentage to be higher in the current study because of better image acquisition standardization.

14.3.4 Image Analysis

We will compare the diagnosis of tumor progression, timing of diagnosis (in months after therapy), and correlations with OS as determined by the various aforementioned imaging methods (i.e., RANO criteria, multiple pMRI metrics). Ultimately, these studies will provide an understanding of how reliably a standardized DSC pMRI sequence can be used in a large prospective clinical trial to differentiate treatment effects from tumor progression. Moreover, by directly comparing several post-processing methods in this large cohort of patients, we will define whether there is an optimal method for evaluating pMRI data in the context of newly diagnosed GBM patients.

We will identify the sensitivity and specificity of Prob-fDMs calculated from pre- and post-treatment within the pre- or post-treatment contrast enhancing lesions to correctly identify

PTRE/PsP from true tumor progression in patients who have progressed via RANO by 6 months post-treatment using receiver-operator characteristic (ROC) analysis. We will determine whether Prob-fDM changes at the time of RANO-determined PD can provide differentiation between PTRE/PsP and tumor progression. We will also determine whether early changes in Prob-fDMs can predict OS. This will be a retrospective analysis on the imaging data. Therefore, true progression vs. pseudoprogression will be determined by serial imaging and use of a confirmatory scan. For example, if a patient has early progression on MRI, the current study will require an additional MRI scan to confirm progressive disease. If this confirmatory scan does not show disease progression, this patient will be categorized as having pseudoprogression

We will co-register the ADC and rCBV maps, as well as conventional imaging types (T2 and Pre/Post T1s) using the T1-Post contrast image as the template. We will then create a 5-dimensional plot of intensities. We will look for differences in the clusters between patients that progress versus those with treatment effects. The number of subjects in each category will be determined by the subjects enrolled and the effectiveness of therapy. In

addition, we will manually evaluate threshold values for rCBV/ADC based on the hypothesis that true progression will be reflected by high rCBV and low ADC (due to cellularity), and thus the highest ratio. We will perform a sensitivity analysis to determine the optimal threshold for the population of subjects available to us. From this analysis, we will define whether analysis of pMRI and DWI can be optimally combined to provide a clearly superior predictor of ultimate tumor progression compared to either measure alone.

14.3.5 Statistical Design

The primary goal of this imaging analysis is to evaluate whether DWI and/or DSC imaging can be used to more reliably differentiate pseudoprogression from true progression in patients treated either with TMZ + placebo or TMZ + veliparib. Thus, for the purposes of this analysis, patients exhibiting progression or pseudoprogression on either arm will be combined for this analysis. Predicting how many patients will have true progression vs. pseudo progression is difficult since a study like this has not been performed (e.g. MGMT methylated + new drug). Based on data from the AVAglio trial (Chinot, NEJM, 2014), the placebo arm suggests 216/463 (46.7%) of patients had progressed by 6 months, for which 43/463 (9.3%) had pseudoprogression, or 43/216 (20%) of early progressors. Extrapolating these results to the current study of 400 patients, we might anticipate 187 patients will have progressed via RANO by 6 months post-treatment. If we assume the same rate of pseudoprogression across both arms, and assume this is equal to the rate of pseudoprogression in the placebo arm in the AVAglio trial (~20%), this will result in approximately 37 patients across both arms with confirmed pseudoprogression (37/187).Using ROC analysis with 150 true progressors versus 37 psuedoprogressors, a two-sided test will have at least 74% power at the 5% significance level to detect an effect size of 0.10 increase in the area under the ROC curve between RANO and DSC/DWI. This power was determined using the R function power.roc.test found in the pROC package. The computation for the amount of power is based on the method developed by Obuchowski (79). The AUC of the two ROC curves (one based on RANO and the other based on DSC/DWI) will be compared with the R function roc.test from the R package pROC. We will use the bootstrap method for obtaining the p-value for the comparison.

We will explore the association between imaging metric¹s diagnosis of tumor progression and OS. Specifically, we will classify patients as highly sensitive based upon an OS greater than the median in a specific arm. For each imaging metric, we will calculate an ROC curve demonstrating its ability to predict highly vs. less sensitive patients. An area under the curve (AUC) will be calculated for each imaging metric and compared using the methods proposed by DeLong (35). The null hypothesis is two ROC curves are equivalent. Again, these areas will be compared using the function roc.test in the R package pROC and we will use the bootstrap value.

We will explore the correlation between time to progression (TTP) and OS. First, time to progression determined by different imaging metrics will be estimated using Kaplan-Meier method and be compared using a bootstrap test because there will be some correlation between the curves. Second, for each imaging metrics, association between TTP and OS will be evaluated using a landmark analyses (with Cox proportional hazard models) at different time points, and time-dependent survival analysis (again using Cox models) where progression will be treated as a time-dependent variable. Model fitting statistics obtained from each time-dependent survival analysis will be compared to select the best imaging metric or metric combinations in predicting OS.

We will compare DSC-MRI and DW-MRI predictions of OS with that of RANO as c-indices. In addition, we plan to compare the time required to achieve a diagnosis by DSC-MRI/DWI-MRI with that by RANO diagnosis. Typically, RANO criteria require serial exams (over several months) to gauge progression/resolution of conventional MRI lesions, while DSC-MRI/DWI-MRI can provide diagnostic information based on single exam time points. So based on these two approaches, we expect that DSC-MRI and DWI-MRI will provide quicker diagnoses that are as accurate (if not more accurate) at predicting OS when compared to RANO.

15.0 General Regulatory Considerations and Credentialing

15.1 Institutional credentialing

Prior to the pre-registration of the first patient, the Imaging and Radiation Oncology Core (IROC) must approve institutions to participate in the A071102 imaging study.

If a site was already credentialed before by the IROC for participate in other CALGB and Alliance imaging studies, the IROC will provide a brief A071102 protocol refresher only to the site prior to the first patient enrollment. Otherwise if a site was never credentialed before by theIROC , the site needs to submit the brain MRI (and/or CT) imaging data of either the baseline of the first subject or any local clinical patients to the IROC for a quality check. The IROC will provide a brief A071102 protocol refresher, and if necessary followed with a virtual site visit, to the site to complete the site credentialing process.

The IROC confirms data receipt within 24 hours, performs quality check of the images with identifying any non-compliant exams that have protocol deviations, and notifies sites of the quality check report within 72 hours upon data receipt.

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Appendix I: Definition of Standard RT/TMZ

Patients are only eligible for this trial if they have completed conventional standard of care treatment for WHO Grade IV gliomas and adequately recovered from treatment related toxicities (CTCAE v4.0 grade 2 or less). The patient must have undergone MRI based treatment planning (CT with contrast-based planning only if patient unable to undergo MRI). At a minimum, the contrast enhancing lesion (and/or surgical cavity) defined on a T1-weighted image (gross tumor volume; GTV) must be targeted with a minimum of a 1 cm dosimetric margin expansion to define a planning target volume (PTV). This volume must have been treated to a prescribed dose of 59.4 Gy in 33 fractions or 60 Gy in 30 fractions. Treatment with larger volumes to the contrast enhancing region is acceptable. Treatment or no treatment of the T2/FLAIR abnormality is acceptable. Because this is optional, dosimetric expansion and dose-fractionation for the T2/FLAIR volume are not specified here. The prescribed dose to the T2/FLAIR volume may not exceed 60 Gy. Radiation therapy must be completed within an overall treatment time of less than 52 calendar days.

Prescribed treatment with concomitant temozolomide must be consistent with the FDA package insert. The prescribed dose must be 75 mg/m2 daily for the 6 to 6.5 weeks of radiation therapy. If the patient missed more than 1 week of temozolomide dosing during radiotherapy, then they are not eligible for the trial. Veliparib can accentuate thrombocytopenia induced by temozolomide. Therefore, if patients had a platelet $< 75{,}000/mm^3$ during concomitant temozolomide therapy during radiation, they are not eligible for this trial.

NOTE: CBC should be monitored during chemoradiation and lowest platelet count must be submitted at registration.

Appendix II: Standard MRI Protocols: (*FDA/NBTS/NCI Standardized MRI Protocol*)

3T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Axial/Sagittal		Axial	Axial/Sagittal
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>2500	2100[g]
TE [ms]	100-140	Min	Min		80-120	Min
TI [ms]	2500		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15		90/≥160	10-15
Frequency	≥256	128	256		≥256	256
Phase	≥256	128	256		≥256	256
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm (for 1mm isotropic)		240mm	256mm (for 1mm isotropic)
Slice Thickness	3mm	3mm	1mm		3mm	1mm
Gap/Spacing	0	0	0		0	0
Diffusion Options		*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

Contrast Injection [a]

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
[b] Post-contrast 3D axial T1-weighted images should be collected with identical parameters to pre-contrast 3D axial T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

1.5T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	3D T1 Post[b]
Sequence	TSE[c] – (turbo dark fluid)	EPI[f]	MPRAGE[d,e]		TSE[c]	MPRAGE[d,e]
Plane	Axial	Axial	Sagittal/Axial		Axial	Sagittal/Axial
Mode	2D	2D	3D		2D	3D
TR [ms]	>6000	>5000	2100[g]		>3500	2100[g]
TE [ms]	100-140	Min	Min		100-120	Min
TI [ms]	2200		1100[h]			1100[h]
Flip Angle	90/≥160	90/180	10-15	**Contrast Injection [a]**	90/180	10-15
Frequency	≥256	128	≥172		≥256	≥172
Phase	≥256	128	≥172		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P
FOV	240mm	240mm	256mm		240mm	256mm
Slice Thickness	≤4mm	≤4mm	≤1.5mm		≤4mm	≤1.5mm
Gap/Spacing	0	0	0		0	0
Diffusion Options[i]		b = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Yes-If Available	Yes-If Available	Yes-If Available		Yes-If Available	Yes-If Available
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	5-8 min

[a] 0.1 mmol/kg or up to 20cc (single, full dose) of MR contrast.
[b] Post-contrast 2D axial T1-weighted images should be collected with identical parameters to pre-contrast 2D axial T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[i] Older model MR scanners that are not capable of >2 b-values should use b = 0 and 1000 s/mm^2.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

Appendix III: Advanced MRI Protocols

3T Protocol:

	Ax T2	Ax FLAIR	Ax DWI	3D T1 Pre	DSC-1[a]	DSC-2[a]	3D T1 Post[b]
Sequence	TSE[c]	TSE[c]	EPI[f]	MPRAGE[d,e]	GE-EPI	GE-EPI	MPRAGE[d,e]
Plane	Axial	Axial	Axial	Axial/Sagittal	Axial	Axial	Axial/Sagittal
Mode	2D	2D	2D	3D	2D	2D	3D
TR [ms]	>2500	>6000	>5000	2100[g]	1500	1500	2100[g]
TE [ms]	80-120	100-140	Min	Min	Min	Min	Min
TI [ms]		2500		1100[h]			1100[h]
Flip Angle	90/≥160	90/≥160	90/180	10-15	60	60	10-15
Frequency	≥256	≥256	128	256	128	128	256
Phase	≥256	≥256	128	256	128	128	256
NEX	≥1	≥1	≥1	≥1	NEX=1 (120 Reps) Inject after 30sec (~20 pts)	NEX=1 (120 Reps) Inject after 30sec (~20 pts)	≥1
Frequency Direction	A/P	A/P	R/L	A/P	A/P	A/P	A/P
FOV	240mm	240mm	240mm	256mm (for 1mm isotropic)	240	240	256mm (for 1mm isotropic)
Slice Thickness	3mm	3mm	3mm	1mm	5mm	5mm	1mm
Gap/Spacing	0	0	0	0	0	0	0
Diffusion Options			*b* = 0, 500, and 1000 s/mm^2				
Parallel Imaging	Up to 2x	Up to 2x	Up to 2x	Up to 2x	No	No	Up to 2x
Scan Time (Approx)	3-5 min	4-5 min	3-5 min	5-8 min	3 min	3 min	5-8 min

[a] 0.05 mmol/kg (1/2) dose injection at a rate of 3-5cc/sec. This is run a total of 2x (DSC-1 and DSC-2). Please maximize slice coverage to include the entire lesion as well as normal brain to the skull vertex. The posterior fossa can be excluded from coverage if there are not enough slices to cover the entire brain.
[b] Post-contrast 2D axial T1-weighted images should be collected with equivalent parameters to pre-contrast 2D axial T1-weighted images
[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)
[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.
[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; GE-EPI = gradient echo echo planar imaging; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

1.5T Protocol:

	Ax FLAIR	Ax DWI	3D T1 Pre		Ax T2	DSC[a]	3D T1 Post[b]
Sequence	TSE[c]	EPI[f]	MPRAGE[d,e]		TSE[c]	GE-EPI	MPRAGE[d,e]
Plane	Axial	Axial	Sagittal/Axial		Axial	Axial	Sagittal/Axial
Mode	2D	2D	3D		2D	2D	3D
TR [ms]	>6000	>5000	2100[g]		>3500	1500	2100[g]
TE [ms]	100-140	Min	Min		100-120	Min	Min
TI [ms]	2200		1100[h]				1100[h]
Flip Angle	90/≥160	90/180	10-15		90/180	60	10-15
Frequency	≥256	128	≥172		≥256	128	≥172
Phase	≥256	128	≥172		≥256	128	≥172
NEX	≥1	≥1	≥1		≥1	NEX=1 (120 Reps) Inject after 30sec (~20 baseline points)	≥1
Frequency Direction	A/P	R/L	A/P		A/P	A/P	A/P
FOV	240mm	240mm	256mm		240mm	240	256mm
Slice Thickness	≤4mm	≤4mm	≤1.5mm		≤4mm	5mm	≤1.5mm
Gap/Spacing	0	0	0		0	0	0
Diffusion Options[i]		*b* = 0, 500, and 1000 s/mm^2					
Parallel Imaging	Yes-If Available	Yes-If Available	Yes-If Available		Yes-If Available	No	Yes-If Available
Scan Time (Approx)	4-5 min	3-5 min	5-8 min		3-5 min	3 min	5-8 min

Preload (1/4 Dose) Contrast Injection [a]

[a] 0.025 mmol/kg (1/4) dose injection. A 0.075 mmol/kg (3/4) dose injection will then be injected at a rate of 3-5cc/sec for DSC. Please maximize slice coverage to include the entire lesion as well as normal brain to the skull vertex. The posterior fossa can be excluded from coverage if there are not enough slices to cover the entire brain.

[b] Post-contrast 2D axial T1-weighted images should be collected with identical parameters to pre-contrast 2D axial T1-weighted images

[c] TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

[d] MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) is equivalent to the inversion recovery SPGR (IR-SPGR or Fast SPGR with inversion activated; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[e] A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[f] In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.

[g] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5-15ms for similar contrast.

[h] For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400-450ms for similar contrast.
[i] Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.

Acronyms:
Ax = Axial; ADC = apparent diffusion coefficient. FLAIR = fluid attenuated inversion recovery; DWI = diffusion-weighted imaging; 3D = three dimensional; TSE = turbo spin echo; EPI = echo planar imaging; GE-EPI = gradient echo echo planar imaging; 2DFL = two-dimensional FLASH (fast low angle shot) gradient recalled echo; MPRAGE = magnetization prepared rapid gradient-echo; A/P = anterior to posterior; R/L = right to left; NEX = number of excitations or averages; FOV = field of view

Appendix IV: Fatigue/Uniscale Assessments

Fatigue/Uniscale Assessments

At patient registration, subsequent therapy visits and post treatment follow-up, this form is to be administered by a nurse/CRA/physician, completed by the patient, and recorded on the Fatigue/Uniscale Assessments Form (see Forms Packet).

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

Your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

Your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Appendix V: Patient Measurement Tools

Mini Mental State Examination (MMSE)

Introduction

The Mini-Mental Status Exam could be administered by the physician, a nurse or an assistant trained in the administration of such tools. The person administering the mini-mental status exam needs to be sensitive when the patient shows embarrassment about their inability to answer these questions. Patients should be assured by telling them that this is another way of telling how the treatment is affecting their brain tumor. It also needs to be made clear to the patient that it is very important to get this type of information directly from them. The person administering the test needs to understand that either the correct answer is given or not. There should be no partial credit for answers short of the mark.

The MMSE begins with a graded assessment of orientation to place and time, for which a maximum of 10 points is possible. This is followed by testing two aspects of memory. The first is the immediate recall for three objects presented orally, followed by a serial sevens task which is interposed to assess attention, concentration, and calculation, and also to prevent the individual from rehearsing the three objects previously learned. A maximum of 21 points may be obtained on this section of the test.

The final section surveys aphasia and apraxia by testing functions of naming, repetition, understanding a three-stage command, reading, writing and copying a drawing. There are a maximum of 9 points which may be obtained on this section, for a total possible MMSE score of 30 points.

MMSE Sections

Detailed instructions are included here. A brief form for recording and scoring MMSE answers follows.

Orientation

Ask the patient for the date. Then ask for parts omitted (e.g., “Can you also tell me what season it is?”). Give one point for each correct response.

Ask in turn, “Can you tell me the name of this hospital? Town? Count? (and so on)”. Give one point for each correct response.

Registration

Ask the patient if you may test his/her memory. Then name three unrelated objects, clearly and slowly, about a second for each. After you have said all three, ask the patient to repeat them. This first repetition determines the score. Score one point for each repeated object (0 – 3). If the patient does not repeat all three objects, the tester should repeat the objects (up to a maximum of six times) until the patient can say all three. In cases where a patient cannot learn all three objects in six trials, recall (see below) cannot be meaningfully tested.

When registration if complete, tell the patient, “Try to remember them because I will ask for them in a little while”.

Attention and Calculation

Ask the patient to begin with 100 and count backwards by seven. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the patient will not perform this task, ask him or her to spell the word "WORLD" backwards. The score is the number of letters in correct order (e.g., DLROW five, DLORW – three).

Recall

Ask the patient if he/she can remember the names of the three objects learned in the Registration section. Give one point for each correct answer.

Language

There are six operations in this section.

Naming

Show the patient a wrist watch and ask him/her what it is. Repeat for a pencil. Give one point for each correct naming (0 – 2).

Repetition

Have the patient repeat, "No, ifs, ands, or buts". All only one trial. Given one point for a completely correct repetition.

Three-Stage Command

Place a piece of blank paper in front of the patient and say; "Take this paper in your right hand. Fold the paper in half. Put the paper on the floor". Give one point for each correctly performed command.

Reading

Show the patient the page with the sentence "Close your eyes" (page 2). Ask the patient to read it and do what it says. Since this is not a memory task, the tester may prompt the reader to "do what it says" after the reader reads the sentence. Score one point if the patient actually closes his or her eyes.

Writing

Give the patient the page with the word sentence (page 3) and ask him/her to write a sentence for you. Do not dictate a sentence; it is to be written spontaneously. The sentence should contain a subject and a verb, and should make sense. Ignore minor spelling or minor grammatical errors when scoring. Score one point for a correct sentence.

Copying

Show the patient the page with the intersecting pentagons (page 4). Ask the patient to copy it exactly as it is. Give one point if all sides are preserved and if the intersecting sides from a four sided figure (i.e., ten sides and ten angles).

Special Considerations

The examination is conducted so as to minimize stress for the patient. Errors are not indicated to the patients and, in general, mistakes are not corrected. Refusals are considered to be errors after a minimum of encouragement. Individuals with peripheral impairment such as blindness or restriction of the hands due to arthritis or other peripheral disorders are scored the number correct out of the possible items they could answer given their other non-cognitive impairments. Please note these exceptions on the MMSE and the cover sheet. It is important not to allow your administration of this test to be affected by your perception of why the patient may have responded incorrectly or not at all. That is, the examination should be conducted without the examiner modifying the scoring by assumptions of whether or not the individual was motivated, paying attention, or could understand. For the purpose of the exam, the score indicates a failed performance, not necessarily a failed performance under all conceivable circumstances.

Spencer MP and Folstein MF. The Mini-Mental State Examination. In: PA Keller and LG Ritt (Eds), Innovations in Clinical Practice: A Source Book. Volume 4. Sarasota, FL: Professional Resource Exchange, Inc., 1985, 307-308.

Mini Mental State Examination

Date: *(mm/dd/yyyy)* __ __/__ __/__ __ __ __

_____/5 What is the: (year) (season) (date) (day) (month)?

_____/5 Where are we: (state) (county) (town) (building) (floor)?

_____/3 Learn: “apple, table, penny.” _____# of trials.

_____/5 Subtract serial 7’s (100, 93, 86, 79, 72): or spell “WORLD” backwards.

_____/3 Recall: “apple, table, penny”.

_____/2 Name: “pencil” and “watch”.

_____/1 Repeat: “no ifs, ands, or buts”.

_____/3 “Take this paper in your right hand, fold it in half, and put it on the floor”.

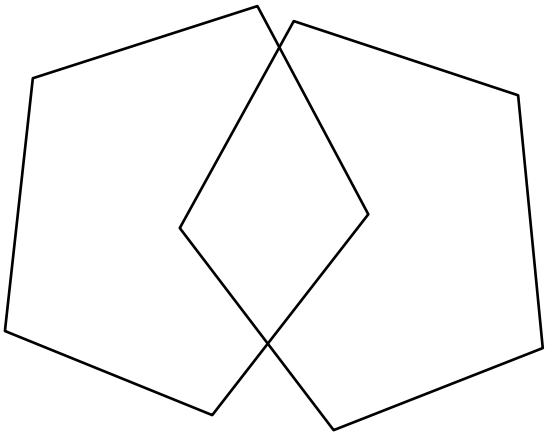
_____/1 Read and obey: “Close your eyes”.

_____/1 Write a sentence on the back of this card.

_____/1 Copy the design on the back of this card.

_____/30 Total (abnormal if <24; if <8th grade, then <21 is considered abnormal)

Close your eyes.



Appendix VI: Patient Medication Diary - Temozolomide

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **temozolomide**.
2. You will take your dose of **temozolomide** on **days 1-5**
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken	Comments
1				
2				
3				
4				
5				
6	**NO MEDICATION ON DAYS 6 THROUGH 28**			
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's Signature Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

Appendix VI: Patient Medication Diary – Veliparib/placebo

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **veliparib/placebo**
2. You will take your dose of **veliparib/placebo twice daily** on **days 1-7**.
3. Record the date, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily dose	# of capsules taken	Comments
1		_____ AM /_____PM	_____ AM /_____PM	
2		_____ AM /_____PM	_____ AM /_____PM	
3		_____ AM /_____PM	_____ AM /_____PM	
4		_____ AM /_____PM	_____ AM /_____PM	
5		_____ AM /_____PM	_____ AM /_____PM	
6		_____ AM /_____PM	_____ AM /_____PM	
7		_____ AM /_____PM	_____ AM /_____PM	
8	**NO MEDICATION ON DAYS 8 THORUGH 28**			
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's Signature Date

Physician's Office will complete this section:

1. Date patient started protocol treatment
   _____
2. Date patient was removed from study
   _____
3. Total number of capsules taken this month (each size)
   _____
4. Physician/Nurse/Data Manager's Signature
   _____

APPENDIX VII: MGMT Assay Description

Central Laboratory Assessment for Hypermethlyation of the Promoter of the O^6-MethylGuanine DNA Methyltransferase (*MGMT*) Gene by Real-Time PCR

The standard method for analysis of MGMT promoter methylation relies on methylation-specific PCR (MS-PCR) using bisulfite converted DNA. The assay was initially reported by Herman et al and is performed commercially in the United States by LabCorp (72). The assay was utilized in the retrospective analysis of EORTC 22981 to demonstrate a benefit to MGMT promoter methylation for patients treated with concurrent TMZ and RT (77). MGMT promoter methylation has been evaluated in two large, multicenter trials prospectively: the RTOG 0525 trial comparing standard dose vs. dose-dense TMZ in the adjuvant treatment of newly diagnosed patients with GBM (76) and the RTOG 0825 trial assessing the role of bevacizumab for patients with newly diagnosed GBM (75). Both trials stratified patients based on MGMT status using the same assay as that planned for the current study. For RTOG 0525, a total of 833 patients were randomized and MGMT status was determined to be hypermethylated in 245 tumors (29%), unmethylated in 517 tumors (62%). 91% of registered patients had tumors for which MGMT status could be determined. Median survival for methylated patients was significantly longer (22 months) as compared to the unmethylated patients (14 months). Similarly, for RTOG 0825, 621 patients were randomized and methylation status determined in 604 cases. A total of 175 (28%) were methylated and 429 (69%) were unmethylated. Median survival was 23.2 months vs. 14.3 months for the methylated vs. unmethylated patients. Based on these prospective, multicenter cooperative group trials, we anticipate MGMT methylation in approximately 30% of cases.

For this clinical trial, the MGMT assay will be performed as initially described by Esteller et al (73) and as modified for real time PCR product detection using a modified amplification primer with a capture sequence to a standard probe for real time detection in a single-step reaction (78). This approach is identical to that used by Labcorp. Following central pathology review at the Mayo Clinic, 10 unstained formalin-fixed, paraffin-embedded (FFPE) tumor sections will be obtained with areas of viable tumor identified. Slides will be transferred to the MDACC CLIA MDL via a BioMS shipping manifest for prospective analysis of MGMT status. DNA will be prepared using the MasterPure Complete DNA and RNA purification kit (Epicentre Biotechnologies, Madison, WI) following deparaffinization using Citrisolve (Amity International, Anderson,SC). Bisulfite conversion of 1 µg of DNA will be performed (Zymo EZ96 DNA methylation kit, Zymo Research) and the remainder of tumor DNA will be frozen at -20C and kept for repeat analyses of MGMT if necessary and for future genomic analyses.

Amplification of bisulfite-modified DNA will encompass the standard enhancer region within the first intron of *MGMT* as previously described (74), generating a 136bp amplicon derived from positions 131155505-131155619 (RefSeq NM_002412) on chromosome 10. PCR primer sequences are as published (78) and included a tagging sequence in the forward primers for real-time detection with the AmpliFluor reagent (Millipore). Reactions are carried out in 15µl volumes and cycled as follows: 50°C for 2 minutes, 95°C for 10 minutes, and 45 cycles of 95°C for 15 seconds and 62°C for 1 minute. The assay detects the difference in amplification between methylated and unmethylated cytosine residues within the specific primer sequences. Conversion of unmethylated cytosines to uracil (thymidine) by sodium bisulfite treatment leads to a sequence change that can be detected using specifically designed PCR primers.

Amplification will be performed using real-time PCR in an Applied Biosystems 7500 Fast Real-Time PCR system. A ΔC_T, defined as the difference in the cycle in which the detected amplification curve (on a log-linear plot) crosses an empirically determined threshold (set for each batch based within the geometric region of amplification) between the MGMT amplicon and the reference *ACTB* amplicon. Control

methylated and unmethylated DNAs will be used with each batch. A ΔC_T of greater than 8 cycles (>256 fold difference) indicates the presence of promoter methylation. A ΔC_T >8 cycles will be coded as unmethylated.

All reactions are carried out in triplicate from replicate bisulfite converted DNA preparations. Discordant results are repeated (including bisulfite conversion when sufficient DNA is available). Cases in which discordant results persist after repeated assays or for which amplification fails secondary to poor quality DNA (or other technical reasons) will be coded as failures/no data.

Assay validation

To validate the assay at MD Anderson using the assay described above, a set of 253 primary GBMs were evaluated for MGMT methylation. Consistent with prior reports, median survival for patients with tumor MGMT hyper-methylation was significantly longer (149 weeks) compared to patients with tumor MGMT unmethylated status (58 weeks).

Further direct comparison of the assay was performed using samples from RTOG 0525, as this tumors had been evaluated by the LabCorp assay. A total of 184 tumors were re-evaluated and concordance between the MD Anderson assay and the LabCorp assay was 97%. Overall sample failures were 9.2%. Sensitivity for MGMT methylation 94% and specificity was 98%. The positive predictive value for the assay was 95.7% and the negative predictive value was 97.5%.

Appendix VIII: Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).-Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human

subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.