Quantitative MRSI to Predict Early Response to Standard RT/Temozolomide ± Belinostat Therapy in Newly-Diagnosed Glioblastomas

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Belinostat, NSC 726630, Spectrum Pharmaceutical supplied, meets criteria for IND waiver
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DISCLAIMER STATEMENT

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ABSTRACT

Glioblastoma (GBM) is the most common primary brain tumor and is uniformly fatal despite aggressive surgical and adjuvant therapies. Since survival is short, it is critical to determine the value of therapy early during treatment. Improved early predictive assessment would allow treating physicians to adjust or change treatment sooner to maximize use of the most effective therapy. During carcinogenesis, tumor suppressor genes can be silenced by aberrant histone deacetylation. This epigenetic modification has become an important target for tumor therapy. Histone deacetylase inhibitors (HDACis) have clinical effects that may include tumor control and cerebral biochemical alterations that may improve mood, correcting the depressive symptoms experienced by many of these brain tumor patients. A phase II clinical trial of vorinostat (an orally available HDACi) in newly diagnosed and recurrent GBM was completed by the NCI-funded North Central Cancer Study Group (NCCTG) and Adult Brain Tumor Consortium (ABTC) and results have been reported in abstract form at ASCO 2014 although a full report of the findings have not yet been published in the peer-reviewed literature. Overall, while this trial did not show an improvement in overall survival compared with historical controls, it is important to note that these results were on unselected patients. Alternative potent HDACis are also currently under evaluation including belinostat (trade name Beleodaq) with pre-clinical activity using *in vivo* GBM models that is at least similar to if not greater than that seen with vorinostat (Shim, H., unpublished data, 2014) potentially making these other drugs a more attractive choice for further investigations in newly diagnosed GBM patients. Due to serious issues of pseudoprogression and pseudoresponse in brain tumor imaging, progression free survival that is determined by contrast-enhanced MRI is unreliable. Frequent histological evaluation is impractical for GBM due to the risks of invasive biopsies and unreliable endpoints. Another problem is that response to HDACi therapy is associated with tumor redifferentiation/cytostasis rather than tumor size reduction, limiting the use of traditional imaging methods in addition to pseudoprogression often occurs in 40% of GBM patients who get treated with the standard adjuvant therapies (radiation and temozolomide). We propose to fill this void by using high resolution, state-of-art 3-dimentional magnetic resonance spectroscopic Imaging (MRSI) method to assess the metabolite profiles as biomarkers noninvasively and longitudinally. In this protocol, we seek to evaluate whether MRSI can predict early response to belinostat therapy in combination with standard adjuvant therapies for newly diagnosed GBMs. We hypothesize that belinostat will improve outcomes in 30 – 40% of GBM patients and that improved response to this combination can be predicted by particular changes in the MRSI biomarker signature at an early point during such therapy. Epigenetic drug such as belinostat is a targeted drug. Thus, it is important to find the subpopulation of patients who are likely to benefit from this therapy as early as possible. Our main objective is to determine whether changes in the metabolite profiles detectable by MRSI within the tumor at an early time after initiation of belinostat therapy can predict improved progression free survival. Secondary and exploratory objectives will include determination about whether belinostat therapy impacts other clinical outcomes including overall survival, neurocognitive function, quality-of-life and mood and whether MRSI can predict response in these areas. Establishing reliable MRS biomarkers to assess early response to standard therapy with belinostat would clearly be of value in personalizing the management of GBM patients by potentially allowing clinicians to seek alternative treatments at an earlier time.

STUDY SCHEMA

Registration

Confirm patient eligibility. 1st 14 patients assigned to **cohort 1** (standard RT/tmz, Emory and JHU) followed by entry to either cohort 1 (until 30 patients total enroll, Emory and JHU) or cohort 2a (standard RT/tmz + dose finding for belinostat up to 12 patients, Emory and JHU) followed by assignment to **cohort 2b** (standard RT/tmz + tolerable dose of belinostat until 45 patients total enroll, Emory and JHU)

⇓

Baseline imaging

MRSI in 14 day window (days -13 to 0) prior to start RT/tmz for the standard therapy cohort (**cohort 1**) or 7 day window (days -6 to 0) prior to belinostat for the belinostat cohorts (**cohorts 2a and 2b**)

⇓

Initial one week drug window (cycle 0, belinostat cohort (cohort 2a and 2 b) only)

Belinostat alone, days 1 through 5 (the latest time to begin therapy at the start of the 6th week, or 36th day from surgery)

MRSI on day 8 (from start of belinostat), or day 1 of cycle 1

⇓

Concurrent chemoradiation phase of therapy (cycle 1, starting day 1 for cohort 1 and starting day 8 for cohort 2a or 2b)

RT to 60 Gy over six weeks (5x/week, Mon-Fri, 30 total treatments) with concomitant daily temozolomide (75mg/m^2/day, 7x/week, Mon-Sun, 42 total doses) for the standard therapy cohort (**cohort 1**) and + belinostat (dose tbd, given IV on days 22-26 and 43-47 from start of therapy, or days 15-19 and 36-40 of cycle 1) (**cohorts 2a and 2b**)

MRSI after 2 weeks of RT/temozolomide ± belinostat (belinostat cohorts will receive 5 days of belinostat alone prior to starting RT/temozolomide)

⇓

Rest period (4 weeks)

Standard MRI (with gadolinium) and MRSI in one week window prior to starting adjuvant temozolomide (in 4th week after completion of radiation)

⇓

Adjuvant phase of therapy (cycles 2-7, every 28 days, may treat up to cycle 13 at physician discretion)

Adjuvant temozolomide (150-200mg/m^2/day, days 1-5 of each cycle)

⇓

Follow up schedule

Initially at 4 weeks post-radiation then prior to every even-numbered cycle (every 2 months x up to 1 year) then every 3 months x 2 years. Subsequent follow up schedule will be determined by patient's physician. Standard MRI (with gadolinium) will be obtained with each follow up visit.

1.0 INTRODUCTION AND BACKGROUND

1.1. Glioblastomas (GBMs)

GBMs are the most common primary brain tumor in adults. Despite optimal management with maximal surgery followed by focal radiation therapy with concurrent and adjuvant temozolomide chemotherapy, patients do poorly with only 10% surviving 5 years [1]. It is clear that current therapeutic approaches to GBM are limited by both acquired and inherent tumor resistance, which can be attributed to many factors including presence of the blood-brain barrier and tumor hypoxia. Because of rapid tumor growth, the blood flow to GBM is not enough to meet the oxygen demand required despite the tumor's attempt to re-vascularize itself through angiogenesis, resulting in the characteristic features of necrosis and microvascular hyperplasia [2]. Because of this variation in tissue integrity and vascularity, drug delivery is expected to be extremely heterogeneous in GBM.

1.2 HDAC inhibitor

Current therapeutic approaches to glioblastoma (GBM) have been disappointing, likely due in part to tumor resistance arising from genetic mutations and aberrant gene expression. Histone acetylation is an important mechanism involved in both normal and abnormal gene expression. This epigenetic modification (i.e., heritable changes of gene expression that do not result from DNA sequence alterations) is now recognized as a frequent change in early phases of tumorigenesis, playing an important role in tumor development. Epigenetic alterations differ significantly from genetic modifications in that they may be readily revertible by ''epigenetic drugs''. These compounds, such as inhibitors of histone deacetylases (HDAC), display pleiotropic activities, including the ability to restore defective gene expression involved in cell cycle control, apoptosis, growth signaling, invasion/metastasis, angiogenesis and immune recognition [2]. Therefore, HDACs are considered to be among the most promising targets in drug development for cancer therapy, and first generation HDAC inhibitors (HDACi) are currently being tested in phase I/II clinical trials [3]. HDAC inhibitor should be one of combination drugs for a subpopulation of GBM patients and a non-invasive imaging tool to predict early response to this will be crucial for successful clinical trial of epigenetic drugs.

Belinostat (trade name Beleodaq, Spectrum Pharmaceuticals) is an active, potent inhibitor of HDACs with activity mainly across class I and II members of this family. As a wide spectrum HDACi, belinostat (PXD101) was initially identified as a novel hydroxamate inhibitor of histone deacetylase activity in HeLa cell extracts with an IC50 of 27 nM [4]. Growth inhibitory activity was noted on a range of tumor cell lines both In vitro (clonogenic and apoptosis assays) with IC50s in the 0.2-3.4 μM range and in vivo tumor growth delay in xenograft models with dosing in the 10-40 mg/kg/day IP range [4]. Since this initial evaluation, belinostat has been extensively evaluated in a number of tumor models that led to numerous clinical trials evaluating its activity in a variety of cancer types. This effort has culminated in the FDA approval of belinostat in 2014 for treatment of relapsed/refractory peripheral T-cell lymphoma. Importantly for brain tumor investigations, belinostat can cross the blood-brain-barrier (BBB) [5].

Among the pleiotropic effects of HDACi is the ability to attenuate inflammation, an action seen at concentrations lower than those required to slow cancer cell growth [6]. GBM is

frequently associated with neuroinflammation, which is thought to have pro-tumorigenic effects. Hypoxic and necrotic regions of GBM are most highly associated with inflammatory cell infiltrates and gene expression profiling reveals a signature associated with hypoxia-inducible genes involved in angiogenesis and inflammation. Such changes are associated with recruitment of macrophages along a hypoxia-mediated chemotactic gradient. Macrophages recruited to hypoxic sites exert tumor-promoting effects through the expression of genes with mitogenic, angiogenic, and migration/invasion stimulating properties [7, 8]. Abrogating inflammatory changes associated with GBM might cut off access to these tumor-promoting effects.

Another intriguing effect of HDACi as an anti-cancer agent is its mood-altering properties as an anti-depressant. In mice, altered patterns of histone acetylation are noted as an adaptive response following chronic social defeat stress, with similar findings in depressed humans on post-mortem exam [9]. Moreover, infusion of HDACi into mouse brains exerted potent antidepressant effects. This is highly relevant given the high frequency of depression (15-39%) in brain tumor patients [10]. In this patient population, depression is consistently associated with cognitive impairment, reduced physical function and poor quality-of-life [11]. Anti-depressant effects of HDACi may be due to their anti-inflammatory properties, given the recent data implicating inflammation with development of depression [12]. Indeed, inflammatory cytokines can interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function and neural plasticity [13, 14]. As noted above, GBMs are infiltrated with inflammatory cells, including macrophages. While their presence and clinical depression have not been correlated, these findings are suggestive and worth exploring.

1.3 Imaging tools

Non-invasive methods of assessing GBM response to therapy *in vivo* are desperately needed, as current imaging techniques do not reliably distinguish tumor progression from changes produced by surgery and radiation. Magnetic resonance spectroscopic imaging (MRSI) is a promising technique that characterizes regions of brain based on presence of specific metabolites. Spectra from GBM differ from normal brain, with increased levels of choline (Cho) and lactate (Lac), and decreased levels of N-acetyl aspartate (NAA). Another important compound is myo-Inositol (MI), a carbocyclic polyol that is the precursor of a number of secondary messengers in eukaryotic cells, including inositol phosphate lipid derivatives. MI is synthesized from glucose-6-phosphate (G-6-P) in two steps: 1) G-6-P is isomerised by inositol-3-phosphate synthase (ISYNA1 or MIP) to inositol-1-phosphate (I-1-P) and2) I-1-P is dephosphorylated by IMPase1 to give free MI [15, 16]. In addition to decreased MI in cancer cells, the CSF of non-cancer patients with depression shows low MI levels, and treating them with MI significantly improved depressive symptoms [17, 18]. The histone deacetylase RPD3 can directly regulate MIP and affect cellular MI levels [19], suggesting that belinostat may also affect MI metabolism, potentially reversing changes associated with malignancy and/or depression. Collectively, these data suggest that MI could be a biologic biomarker to quantify response to belinostat.

Determining brain tumor type and grade requires histopathological examination of a surgical specimen, which, in some locations, may entail significant risk of morbidity or even mortality to obtain. GBMs are inherently heterogeneous, comprising a combination of viable tumor of various grades with necrotic tissue as well as infiltration of normal brain. Glial scar and

radiation changes can be mistaken for tumor recurrence. The current standard for assessing tumor progression relies on changes in size of the enhancing and/or nonenhancing components of the tumor on standard MRI. However, standard MRI is increasingly recognized as insufficient because of the development of "pseudoprogression." While "pseudoprogression" may occur even in GBM patients treated with radiation alone, the addition of temozolomide has significantly increased the incidence of "pseudoprogression" while the use of anti-angiogenic agents (e.g. cediranib) has increased the incidence of "pseudoresponse" complicating the interpretation of standard imaging. Increasing use of newer, molecularly-targeted agents may further decrease the reliability of MRIs. Alternative imaging modalities (ie. MR perfusion, PET, etc.) may provide complementary information but have not been widely adopted to date for a variety of reasons. ^{1}H-MRSI offers a non-invasive means to differentiate tumors from post-treatment changes and to distinguish benign from malignant lesions based on specific MR-detectable metabolite levels without introducing exogenous variables [20-23]. However, in practice, MRSI has not been used to its full potential in the clinical setting due to low spatial resolution, long acquisition times, and insufficient tools for post-processing and display in its current commercially available form. In fact, the quality of MRSI data is often insufficient for clinical use with 'out-of-the-box', vendor-provided sequences. Recent advances in MRSI technology, and recent development of image registration and visualization tools that allow clinicians to evaluate and utilize MRSI data more easily, will clear these hurdles that have made routine clinical application difficult. For this clinical study, we will use high-resolution MRSI sequences to acquire whole brain 3D metabolite ratio maps with 0.1 cc resolution within a reasonable, clinically feasible scan time (~10 minutes), integrate MRSI processing/viewing software with the image registration tools needed to use MRSI effectively in the clinical setting, and initiate a clinical study that seeks to validate the use of MRSI in the clinical management of brain tumor patients. Processing of the MRSI sequences used on this study will be performed by the MIDAS software package kindly provided by the University of Miami (A. Maudsley, consultant on grant). Accordingly, we will share de-identified MRSI data with the University of Miami group regarding data for sequence optimization. The MIDAS software package is investigational but is considered to have a non-significant risk.

1.4 Rationale for combining belinostat with radiation therapy and temozolomide for GBMs

Several lines of evidence suggest a potential for cooperative interaction of the combination of HDAC inhibitors and DNA targeting agents: A) the ability of HDAC inhibitors to alter nucleosome structure and promote a 'relaxed' chromatin conformation can potentially permit better access of DNA targeting agents to the chromatin and increase sensitivity of the cells to these agents. In this context, pretreatment of tumor cell lines *in vitro* with histone deacetylase inhibitors has been shown to sensitize cells to various chemotherapeutic agents or radiation [24, 25]; B) Data presented in the previous sections suggest that the biochemical pathways activated by HDACi in glioma cells are distinct from that of temozolomide but the biologic effects overlap, suggesting a potential for synergy for this combination; and C) Studies by our group evaluating the ability of treatment with vorinostat, another HDACi with a similar range of effects to belinostat, to sensitize the tumorigenic malignant U87MG glioma cell line to temozolomide *in vitro* showed a supra-additive effect on growth inhibition by the combination across the dose range. Similar results were obtained with other chemotherapies in combination with belinostat. Finally, previous determinations in non-human primates suggest that IV dosing of belinostat does not result in significant CSF drug levels [26].

However, more recent evidence does suggest that belinostat is actually capable of crossing the blood-brain barrier (BBB) to a significant extent [5]. Taken together, these results suggest that belinostat may serve as a potential sensitizer of alkylating chemotherapeutic agents and radiation therapy for malignant glioma by increasing their cytotoxic efficacy and can likely reach its GBM target due to demonstrated ability to cross the BBB.

1.5 Significance

Belinostat, as an HDACi, opens up the chromosomes, making them more vulnerable to temozolomide (TMZ), [27] and radiation therapy (RT) [28] (http://www.ncbi.nlm.nih.gov/books/NBK13838). A Phase I trial of vorinostat + TMZ in recurrent GBM has been successfully completed; the patient enrollment of a Phase I/II clinical trial in newly-diagnosed GBM patients have been completed in the NCCTG and ABTC; however, the primary endpoint is overall survival. Thus it will take another year or two to get the results. Our preliminary results evaluating belinostat in a preclinical rat brain tumor model suggest that this drug may have superior activity to vorinostat [29].

Taken together, these results indicate that treatment with belinostat presents an opportunity to (1) induce redifferentiation/cytostasis of tumors, (2) sensitize gliomas to standard XRT + TMZ, and (3) offer symptomatic relief from depression in GBM patients. However, with current limitation of brain tumor imaging due to pseudoprogression/ pseudoresponse, it is extremely difficult to accurately determine progression free survival as an endpoint for any brain tumor clinical trials. Belinostat's mechanism of action and expected changes in tumor metabolism lend themselves to the use of MRSI as a tool for monitoring its effects. We propose to implement state-of-the-art MRSI technology that can generate three-dimensional (3D) metabolite maps of the entire brain in a short time suitable for clinical use (~10 mins). We will also introduce a program that can display MRSI data co-registered with other imaging studies in a clinically useful fashion. Our intended outcome is to make MRSI practical for clinical use, and a part of the standard assessment of brain tumor patients. In the present era of molecularly targeted therapy, when cytotoxicity may not be the primary therapeutic effect, contrast-enhanced MRI has become less effective for monitoring response and progression.

MRSI presents a noninvasive, nondestructive method, which can provide longitudinal pharmacodynamic biomarkers of drug delivery and action at defined anatomic locations in individual cancer patients. Reliable MRS biomarkers associated with early response ("metabolic response") would clearly be of value in personalizing the management of GBM patients by providing clinicians the opportunity to adjust the dose of belinostat or to seek alternative treatment, instead of using overall survival as the primary endpoint. Given that GBM patient survival time is short, it is critical to determine the therapeutic activity at the earliest stage to enable oncologists to make timely changes in treatment.

MRSI is not widely used in clinical practice due to relatively low resolution, long acquisition time, and inefficient forms of data display. By implementing advanced MRSI acquisition and processing methods, we will obtain 3D whole brain metabolite maps with 4 mm in-plane resolution in a clinically acceptable scan time (~10 mins). If this imaging modality can be developed to the point where it can be added to standard-of-care MRIs for GBM patients, this could provide a cost-effective, accurate assessment of treatment response, especially when compared to other imaging modalities, such as PET, which require a separate scanner. Because contrast-enhanced MRI alone cannot always accurately assess cancer therapy

response to RT or differentiation-inducing drugs, use of MRSI may significantly increase diagnostic accuracy in these settings. The comprehensive and state-of-the-art approach to be developed and validated here may provide a better tool for assessing tumor progression than conventional MRI alone. If successful, our methodology can easily be disseminated to other sites performing trials involving HDACis.

2.0 OBJECTIVES

Our main goals are to establish the use of whole brain, high resolution MRSI to evaluate response with standard radiation and temozolomide for newly-diagnosed GBM patients (cohort 1) and to determine the maximal tolerated dose (MTD) of belinostat (cohort 2a) and assess the efficacy of belinostat at MTD (cohort 2b) with standard radiation and temozolomide for newly-diagnosed GBM patients and determine whether MRS-based tools can aid clinicians in the early determination of response to this new therapy. In addition, we are interested in determining whether certain metabolites assessable by MRS can serve as reliable biomarkers of altered mood (depression) in GBM patients (cohorts 1 and 2b) and whether this can be alleviated with belinostat treatment (cohort 2b). Finally, an additional analysis will be performed determining whether certain pretreatment molecular characteristics of GBMs will be predictive of response (by standard MRI and MRSI) (cohorts 1 and 2b).

2.1 Primary Objectives

2.1.1 To utilize machine learning (eg. a support vector machine approach) to determine an MRSI 5-metabolite profile that is predictive of prolonged progression-free survival (PFS at 9 months) at week 3 (during chemoRT) (**Cohort 1**).

2.1.2 To find the MTD of belinostat (up to 1000 mg/day x 5 days q3weeks x 3) used with standard RT/temozolomide for newly diagnosed GBM patients (**Cohort 2a**)

2.1.3 To determine whether MRSI is useful as an early biomarker by comparing progression-free survival (PFS at 9 months) of belinostat-responders versus non-responders based changes in MRSI metabolite maps (SRI > 0.8, see sections 2.3 and 14.5) at week 3 (during chemoRT) (**Cohort 2b**).

2.2 Secondary Objectives

2.2.1 To determine whether changes in MRSI metabolite maps at week 3 are useful as an early biomarker for predicting improved overall survival (OS) at 18 months (**Cohorts 1 and 2b**).

2.2.2 To determine whether changes in MRSI metabolite maps predict for mood alterations as measured by a self-reported depression survey (IDS-SR) (**Cohorts 1 and 2b**).

2.2.3 To determine whether changes in MRSI metabolite maps at day 8 (after initial belinostat window) and week 11 (4 weeks post-concurrent chemotherapy and radiation therapy) correlate with PFS at 9 months and OS at 18 months (**Cohorts 1 and 2b**).

2.2.4 To compare the OS and PFS of patients treated with belinostat/TMZ/RT versus TMZ/RT (**Cohorts 1 and 2b**).

2.3 Exploratory Objectives

2.3.1 To determine whether changes in MRSI metabolite maps correlate with changes in subjects' quality-of-life as measured by validated self-assessment instruments (**Cohorts 1 and 2b**).

2.3.2 To determine whether changes in MRSI metabolite maps correlate with changes in subjects' overall neurocognitive function (**Cohorts 1 and 2b**).

2.3.3 To determine whether pretreatment molecular characteristics of the tumor can predict improved MRSI response and/or outcomes with belinostat/TMZ/RT therapy (**Cohort 2b**).

2.3.4 To determine a good SRI cutoff for a positive response to belinostat. The SRI cutoff of 0.8 (80% change) is just our starting point for assessing this question and was based on preliminary data from the previous Quick Trial (**Cohort 2b**).

3.0 PATIENT ELIGIBILTY

3.1 Minorities and Women: Subjects for all groups will be approximately representative of the demographics of the patient population at Emory University and Johns Hopkins University. This study is designed to include women and minorities, but is not designed to measure differences of intervention effects. While males and females will be recruited with no preference to gender, based results on previous studies, we expect 40% of our accrual to be female. No exclusion to this study will be based on race. Minorities will actively be recruited to participate. However, based on previous enrollment, we do not expect higher than 10% of subjects to be minorities.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	3	=	5
Not Hispanic or Latino	34	+	51	=	85
Ethnic Category: Total of all subjects	36	+	54	=	90
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	2	+	3	=	5
Black or African American	3	+	5	=	8
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	31	+	46	=	77
Racial Category: Total of all subjects	36	+	54	=	90
	(A1 = A2)		(B1 = B2)		(C1 = C2)

Accrual Rate: 3 pts/month **Total Expected Accrual:** 80 Min 90 Max

Projected Start Date of Study: Apr. 1, 2013

3.2 Subject Enrollment

Subjects will be recruited among newly-diagnosed GBM patients referred by neurosurgery, neuro-oncology or radiation oncology. Initial screening will be conducted/reviewed by clinical investigators and/or their designee (e.g. research nurse, research coordinator, etc.) who has been trained. Cases will be identified from the neurosurgery, neuro-oncology and radiation oncology outpatient clinics and neurosurgery inpatient service at each site.

3.3 Patient Selection - Inclusion Criteria:

3.3.1 Patients must have a newly-diagnosed glioblastoma or gliosarcoma that has been confirmed pathologically.

3.3.2 Patients must be ≥ 18 years of age.

3.3.3 Patients must be able to have MRI scans.

3.3.4 Patients must have measurable contrast-enhancing supratentorial tumor (≥ 0.2 cc (current resolution of MRSI is 0.108cc)) in a region amenable to MRSI.

3.3.5 Patient must have the following lab values ≤ 14 days prior to registration:

- WBC ≥ 3,000/μL
- ANC ≥ 1,500/μL
- platelet count of ≥ 100,000/μL
- hemoglobin ≥ 10 gm/dL (transfusion is allowed to reach minimum level)
- SGOT ≤ 2.0x UNL
- bilirubin ≤ 2 x UNL
- creatinine ≤ 1.5 mg/dL

3.3.6 Patients must have a life expectancy of ≥ 12 weeks.

3.3.7 Patients must have a KPS ≥ 60.

3.3.8 Patients who are women of childbearing potential must have a negative beta-HCG pregnancy test documented ≤ 7 days prior to registration.

3.3.9 All men and women of childbearing potential must agree to use adequate barrier contraception for the duration of study participation and for 12 weeks after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she needs to inform her treating physician immediately.

3.3.10 Patients must be able to understand and provide written informed consent.

3.3.11 Both men and women, and members of all races and ethnic groups are eligible for this trial. Subjects will be approximately representative of the demographics of the referral base for the participating institutions.

3.3.12 Patient must be able to swallow capsules.

3.3.13 Patient must be willing to provide mandatory tissue samples (unstained slides) for research purposes.

3.3.14 Patients must be willing to forego other cytotoxic and non-cytotoxic therapies against the tumor while being treated on this protocol.

3.4 Patient Selection - Exclusion Criteria:

3.4.1 Patients with pacemakers, non-titanium aneurysm clips, neurostimulators, cochlear implants, non-titanium metal in ocular structures, history of being a steel worker, or other incompatible implants which makes MRI safety an issue are excluded.

3.4.2 Patients that have any significant medical illnesses that in the investigator's opinion cannot be adequately controlled with appropriate therapy or would compromise the patient's ability to tolerate this therapy are excluded.

3.4.3 Patients with a history of any other invasive cancer (except non-melanoma skin cancer and excluding carcinoma in-situ), unless in complete remission and off of all therapy for that disease for ≥ 3 years, are ineligible.

3.4.4 Patients with an active infection or serious intercurrent medical illness are ineligible.

3.4.5 Patients with any disease that will obscure toxicity or dangerously alter drug metabolism are excluded.

3.4.6 Patients receiving any other investigational agents are excluded.

3.4.7 Patients who have received prior cytotoxic, non-cytotoxic or experimental drug therapies for brain tumor are excluded.

3.4.8 Patients with a history of prior cranial radiation are ineligible.

3.4.9 Patients with a history of myocardial infarction or unstable angina ≤ 6 months prior to registration or congestive heart failure (CHF) requiring use of ongoing maintenance therapy, or life-threatening ventricular arrhythmias.

3.4.10 Patients with congenital long QT syndrome. (for cohort 2a and 2b (belinostat cohorts) only, ECG not required for cohort 1)

3.4.11 Patients with prolonged QTc interval (>450 msec). (for cohort 2a and 2b (belinostat cohorts) only, ECG not required for cohort 1)

3.4.12 Patients taking any of the following Category I drugs that are generally accepted to have a risk of causing Torsades de Pointes ≤ 7 days prior to registration. (for cohort 2a and 2b (belinostat cohorts) only)

- Quinidine, procainamide, disopyramide
- Amiodarone, sotalol, ibutilide, dofetilide
- Erythromycin, clarithromycin
- Chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

3.4.13 Patients taking valproic acid ≤ 2 weeks prior to initiation of belinostat therapy. (for cohort 2a and 2b (belinostat cohorts) only)

3.4.14 Patients with residual enhancing tumor that lies completely within 1-2 cm of the inner table of the skull. Please consult study neuroradiologist or study PIs at your site if there is uncertainty regarding this exclusion criteria.

3.4.15 Patients may not be enrolled on any other therapeutic trial for which they are receiving an anti-tumor therapy. (**Note:** patients on the standard therapy arm of another GBM trial that otherwise meet eligibility requirements for this trial remains eligible for cohort 1)

4.0 PATIENT SAFETY

4.1 Belinostat is an FDA-approved drug for treatment of relapsed/refractory peripheral T-cell lymphoma. Patients will be monitored by a physician during their scheduled visits. The most commonly reported clinical adverse events (AEs) of any grade (> 10% frequency) related to belinostat for patients receiving IV belinostat as monotherapy were nausea (49.8%), vomiting (34.6%), fatigue (27.6%), diarrhea (15.6%), flushing (11.3%), and constipation (10.3%). The most common serious adverse events (SAEs) (≥ 1% frequency) related to belinostat for patients receiving IV belinostat as monotherapy were pyrexia (1.7%), thrombocytopenia (1.7%), nausea (1.3%), and vomiting (1.3%). Adverse events will be managed, as is typical in clinical trials. As adverse event (AE) monitoring and reporting is a routine part of every clinical trial, the standard approach to determining if an AE merits expedited (via AdEERS system at NCI) or routine (via CTMS or CDUS at NCI) reporting will be utilized. Description of toxicity will utilize CTCAE 4.0 as defined at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

4.2 The risks associated with MRSI are the same as those with conventional MRI. Movement or heating of metallic implants is a potential risk, and so subjects will be screened to exclude people with metallic implants, fragments, or pacemakers. Some individuals experience claustrophobic reactions in the scanner. Subjects will be informed of this prior to the study, but because it is difficult to predict who will have such a reaction, this is not a specific exclusion criterion. Any subject experiencing claustrophobia will be removed from the scanner immediately. There is no invasive component to this study and so discomfort, bruising, or infection is not a risk.

There may be additional risks associated with scanning at 3T, which are addressed here:

1. Effect of the static field. The FDA has approved for routine clinical use, scanners up to 4.0 T. The scanners that we will be using are FDA approved. However, the MIDAS software

package is experimental and has been provided through a master research agreement with the University of Miami. There is no conclusive evidence for irreversible or hazardous bioeffects to acute, short-term exposures of humans up to 2.0 T. Studies have indicated some side-effects at 4.0 T, namely unusual sensations including nausea, vertigo, and metallic taste. However, there is no evidence that this is either irreversible or harmful. If subjects experience unusual sensations, they will be withdrawn.

2. Effect of the gradient field. MRI operates by rapidly changing small additional fields, called gradients. By Faraday's induction law, a changing magnetic field will induce electrical currents in any conductor. Thus, rapid cycling of the gradient field can induce peripheral nerve stimulation. However, this is not substantially different at higher magnetic fields since the gradients are separate from the main magnet. If subjects experience peripheral nerve stimulation, e.g. tingling or twitching, they will be withdrawn.

3. Effect of the RF electromagnetic field. The fundamental principle of MRI is that protons are excited by sending in an RF pulse at their resonant frequency for the magnetic field. The FDA provides guidelines for the safe use of MR systems, which includes specific recommendations for how much RF power is safe. The "specific absorption rate", or SAR is the mass normalized rate at which RF power is coupled to biologic tissue and is typically indicated in units of watts per kilogram (W/kg) (NRCP, 1986). The FDA provides recommendations for two alternative safe levels of exposure to RF radiation during MR procedures, primarily to control the risk of systematic thermal overload (heating) and local thermal injury. These are (FDA, 1988):

    a. The exposure to RF energy below the level of concern is an SAR of 0.4 W/kg or less averaged over the body, and 8.0 W/kg or less spatial peak in any 1 g of tissue, and 3.2 W/kg or less average over the head; or

    b. The exposure to RF energy that is sufficient to produce a core temperature increase of 1^{o}C and localized heating to no greater extent than 38^{o}C in the head, 39^{o}C in the trunk, and 40^{o}C in the extremities, except for patients with impaired systemic blood flow and/or perspiration.

We will adhere to the recommendations for the head, which is also monitored by Siemens' built in monitor.

4.3 Temozolomide and Belinostat Related Risks: The risks related to the use of temozolomide and belinostat are outlined in the information below regarding these drugs.

5.0 PHARMACEUTICAL INFORMATION

5.1. BELINOSTAT (trade name Beleodaq)

5.1.1 Belinostat (NSC 726630)

5.1.2 Chemical Name: (E)-*N*-hydroxy-3-(3-(*N*-phenylsulfamoyl)phenyl)acrylamide

5.1.3 Other Names: PXD101

5.1.4 Classification: Antineoplastic

5.1.5 CAS Registry Number: 414864-00-9, 866323-14-0

5.1.6 Molecular Formula: $C_{15}H_{14}N_2O_4S$, M.W.: 318.35

5.1.7 Approximate Solubility: Water 0.14 mg/mL; 1,2-propanediol ~0.2 mg/mL; polyethylene glycol 400, ~1.5 mg/mL; ethanol > 200 mg/mL

5.1.8 Description: Histone deacetylase (HDAC) inhibitor

5.1.9 Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Belinostat is a potent inhibitor of Class I and II HDAC enzymes. It causes G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells.

5.1.10 How Supplied: Belinostat is supplied by Spectrum Pharmaceuticals as a yellow, lyophilized cake containing belinostat and arginine. The product is supplied in single-use 30 mL clear glass vials (500 mg belinostat/vial) with coated stoppers and aluminum crimp seals with "flip-off" caps. The lyophilized product should be reconstituted with 9 mL Sterile Water for Injection to give a belinostat concentration of 50 mg/mL.

5.1.11 Storage and Handling: The lyophilized drug product vials should be stored at controlled room temperature (20-25°C; 68-77°F), with excursions between 15 and 30°C (59 to 86°F) and transient spikes between -20 and 40°C (-4 to 104°F) permitted. The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency and maintenance within the acceptable storage temperature range. Documentation of temperature monitoring should be maintained as per the institutional guidelines. The product should remain in the outer carton until use. After reconstitution with 9 mL Water for Injection the liquid formulation (50 mg belinostat/mL) may be stored at controlled room temperature (20-25°C; 68-77°F) for up to 12 hours. After mixing with 250 mL 0.9 % Sodium Chloride Injection, the resulting dilution of drug product may be stored at controlled room temperature (20-25°C; 68-77°F) for up to 36 hours including infusion time. The admixed drug product solution must be filtered through an FDA (or other applicable non-U.S. Regulatory Agency, for non-U.S. studies) approved 0.22 µm in-line filter or 0.22 µm filter extension set prior to administration. Any unused material must be discarded. The drug product solution or dilutions cannot be mixed with any other drug in the infusion bag or administration set.

5.1.12 Stability: Shelf life stability studies of the intact bottles are ongoing.

5.1.13 Route of Administration: Intravenous

5.1.14 Method of Administration: Each dose will be given intravenously over 30-45 minutes per instructions in package insert.

5.1.15 Potential Drug Interactions: The potential for drug interactions of belinostat and major metabolites were determined *in vitro* in Cytochrome P450 (CYP) inhibition, induction and metabolism studies [30, 31]. Results indicate that belinostat with its

metabolites is a weak/moderate inhibitor of CYP2C8 and moderate to strong inhibitor of CYP2C9. Belinostat is P-glycoprotein **(**P-gp)-substrate, but belinostat does not inhibit P-gp transporters [32].

5.1.16 Special Handling: Belinostat is an anticancer drug. Procedures for proper handling and disposal of anticancer drugs per institution should be used. Direct contact of the lyophilized belinostat drug with the skin or mucous membranes should be avoided. If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules. Clean spills from damaged vials carefully minimizing inhalation. Wash spill area at least 3 times with ethanol followed by water.

5.1.17 Patient Care Implications: Because belinostat's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Encourage patients to seek a nutritional consult.

5.1.18 Adverse Events and Potential Risks for Belinostat (NSC 726630**):** The following tables show AEs and SAEs from 14 NCI-sponsored and 16 company-sponsored trials where belinostat was used either as monotherapy or in conjunction with other anti-neoplastic therapies. Results on the 14 NCI trials (N=457), including monotherapy and combination therapy, are presented together below. Results on the 16 company trials (N=693) are presented in the follow treatment groups: Group I, belinostat IV monotherapy; Group II, belinostat IV with anthracycline; Group III, belinostat IV with 5-FU; Group IV, belinostat IV with paclitaxel and/or carboplatin; Group V, belinostat IV with bortezomib; Group VI, belinostat IV with CHOP; and Group VII, belinostat oral monotherapy. More details about toxicities attributable to belinostat based on the experience from clinical trials can be found in the Investigator's Brochure (version 11.0, date 5/23/2014). The final table is a listing of serious adverse events terms, related to belinostat, that for regulatory reporting purposes are considered to be expected based on previous company-sponsored trials.

NCI Safety Data for Belinostat (NSC 726630)

From Annual Report to NCI (August 2013)

Most Frequent Related AEs Occuring in ≥ 12% of Patients from NCI Annual Report*

Adverse Reactions	Organ system	% (N=455)
Nausea	Gastrointestinal disorders	60
Fatigue	General disorders and administration site conditions	50
Vomiting	Gastrointestinal disorders	42
Anemia	Blood and lymphatic system disorders	39
Platelet count decreased	Investigations	30
WBC decreased	Investigations	28
Neutrophil decreased	Investigations	27
Lymphocyte decreased	Investigations	27
Anorexia	Metabolism and nutrition disorders	22

Diarrhea	Gastrointestinal disorders	18
Constipation	Gastrointestinal disorders	17
ECG QTc interval prolonged	Investigations	16
Injection site reaction	General disorders and administration site conditions	16
AST increased	Investigations	12
Dizziness	Nervous system disorders	12
* Includes all adverse experiences occurring in ≥ 12% of patients and considered possibly, probably, or definitely related to the study therapy by the Principal Investigator		

Most Related SAEs from NCI Annual Report*

Organ System	Related Serious Adverse Event	Total # of Patients Treated (N=455)		
		Gr. 3 %	Gr. 4 %	Gr. 5%
Blood and lymphatic system disorders	Anemia	11	<1	--
	Blood and lymphatic system disorders - Other, specify	<1	--	--
	Febrile neutropenia	3	--	<1
	Leukocytosis	<1	--	--
Cardiac disorders	Acute coronary syndrome	<1	--	--
	Atrial fibrillation	<1	--	--
	Heart failure	<1	--	--
	Left ventricular systolic dysfunction	<1	--	--
	Sinus bradycardia	<1	--	--
	Sinus tachycardia	<1	--	--
	Supraventricular tachycardia	<1	--	--
Ear and labyrinth disorders	Hearing impaired	<1	--	--
Eye disorders	Eye disorders - Other, specify	<1	--	--
Gastrointestinal disorders	Abdominal pain	<1	--	--
	Colonic obstruction	<1	--	--
	Diarrhea	1	--	--
	Mucositis oral	<1	--	--
	Nausea	3	--	--
	Rectal hemorrhage	<1	--	--
	Small intestinal obstruction	<1	--	--
	Upper gastrointestinal hemorrhage	--	--	<1
	Vomiting	3	--	--
General disorders and administration site	Death NOS	--	--	<1
	Edema limbs	<1	--	--
	Fatigue	4	--	--
	Non-cardiac chest pain	1	--	--

conditions	Sudden death NOS	--	--	<1
Immune system disorders	Allergic reaction	<1	<1	--
	Anaphylaxis	1	<1	--
Infections and infestations	Catheter related infection	1	--	--
	Enterocolitis infectious	<1	--	--
	Infections and infestations - Other, specify	2	--	<1
	Lung infection	1	--	<1
	Salivary gland infection	--	<1	--
	Skin infection	<1	--	--
	Urinary tract infection	1	--	--
Investigations	Activated partial thromboplastin time prolonged	<1	--	--
	Alanine aminotransferase increased	2	--	--
	Alkaline phosphatase increased	<1	--	--
	Aspartate aminotransferase increased	2	--	--
	CPK increased	--	<1	--
	Cardiac troponin I increased	<1	--	--
	Cholesterol high	<1	--	--
	Creatinine increased	1	--	--
	Ejection fraction descreased	<1	--	--
	Electrocardiogram QT corrected interval prolonged	4	--	--
	INR increased	<1	--	--
	Lymphocyte count decreased	9	8	--
	Neutrophil count decreased	7	12	--
	Platelet count decreased	7	9	--
	Weight gain	<1	--	--
	White blood cell decreased	9	7	--
Metabolism and nutrition disorders	Anorexia	1	--	--
	Dehydration	1	--	--
	Hyperglycemia	<1	--	--
	Hyperkalemia	<1	--	--
	Hypermagnesemia	2	--	--
	Hypertriglyceridemia	<1	<1	--
	Hyperuricemia	--	<1	--
	Hypoalbuminemia	1	--	--
	Hypocalcemia	1	--	--
	Hypokalemia	3	--	--
	Hypomagnesemia	<1	--	--

	Hyponatremia	2	--	--
	Hypophosphatemia	4	--	--
	Tumor lysis syndrome	<1	--	--
Musculoskeletal and connective tissue disorders	Arthralgia	<1	--	--
	Bone pain	<1	--	--
	Generalized muscle weakness	<1	--	--
	Musculoskeletal and connective tissue disorder - Other, specify	<1	<1	--
	Pain in extremity	1	--	--
Nervous system disorders	Dizziness	<1	--	--
	Headache	<1	--	--
	Syncope	1	--	--
Renal and urinary disorders	Acute kidney injury	<1	<1	--
	Hematuria	<1	--	--
Respiratory, thoracic and mediastinal disorders	Dyspnea	<1	1	--
	Hypoxia	1	<1	--
	Pneumonitis	--	<1	--
	Pulmonary edema	<1	--	--
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome	<1	--	--
	Rash maculo-papular	<1	--	--
	Urticaria	<1	--	--
Vascular disorders	Hematoma	--	<1	--
	Hypertension	1	--	--
	Hypotension	<1	<1	--
	Thromboembolic event	1	--	--
	Vascular disorders - Other, specify	<1	--	--
* Includes all adverse experiences considered possibly, probably, or definitely related to the study therapy by the Principal Investigator.				

AEs with a Frequency ≥ 10% (≥ 30 Patients) in Group I - Belinostat IV Monotherapy

	Total Study Population, N=301			
	AEs Related to Belinostat	AEs Related to Belinostat	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse Event (MedDRA PT*)	No Pts** (%)	No Pts** (%)	No Pts** (%)	No Pts** (%)
Nausea	150 (49.8%)	3 (1.0%)	176 (58.5%)	5 (1.7%)
Vomiting	104 (34.6%)	2 (0.7%)	117 (38.9%)	3 (1.0%)
Fatigue	83 (27.6%)	8 (2.7%)	127 (42.2%)	17 (5.7%)
Diarrhea	47 (15.6%)	2 (0.7%)	80 (26.6%)	5 (1.7%)
Flushing	34 (11.3%)	0 (0.0%)	36 (12.0%)	0 (0.0%)
Constipation	31(10.3%)	2 (0.7%)	94 (31.2%)	4 (1.3%)

Source: ae-clindb-cut-off-30nov2013 *: PT=MedDRA Preferred Term, **: Pts=patients

SAEs, Related to Belinostat, Reported in ≥ 2 Patients in Group I - Belinostat Monotherapy (N=301)

No. of Cases in 301 Patients	MedDRA Preferred Term	CTCAE Grade	MedDRA SOC
5	Pyrexia	Grade 2: 3 events Grade 1: 2 events	General disorders and administration site conditions
5	Thrombocytopenia	Grade 4: 4 events Grade 3: 1 event	Blood and lymphatic system disorders
4	Nausea	Grade 3: 1 event Grade 2: 1 event Grade 1: 2 events	Gastrointestinal disorders
4	Vomiting	Grade 3: 2 events Grade 2: 1 event Grade 1: 1 event	Gastrointestinal disorders
3	Blood creatinine increased	Grade 2: 2 events Grade 1: 1 event	Investigations
3	Pneumonia	Grade 3: 3 events	Infections and infestations
3	Infection	Grade 3: 3 events	Infections and infestations
2	Anaemia	Grade 4: 1 event Grade 3: 1 event	Blood and lymphatic system disorders
2	Azotaemia	Grade 4: 2 events	Renal and urinary disorders
2	Constipation	Grade 3: 1 event Grade 2: 1 event	Gastrointestinal disorders
2	Fatigue	Grade 3: 1 event Grade 2: 1 event	General disorders and administration site conditions
2	Sepsis	Grade 3: 2 evetns	Infections and infestations
2	Vasculitis	Grade 3: 2 events	Vascular disorders

Source: sae-pvdb-cut-off-30nov2013

AEs with a Frequency ≥ 10% (≥ 9 Patients) in Group II – Belinostat IV in Combination w/Anthracycline

	Total Study Population, N=82			
	AEs Related to Study Drug	AEs Related to Study Drug	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse Event (MedDRA PT*)	No Pts (%)	No Pts (%)	No Pts (%)	No Pts (%)
Nausea	46 (53.5%)	3 (3.7%)	60 (73.1%)	4 (4.9%)
Vomiting	39 (47.6%)	0 (0.0%)	49 (45.1%)	0 (0.0%)
Fatigue	35 (42.7%)	6 (3.7%)	49 (40.2%)	8 (4.9%)
Alopecia	29 (35.3%)	0 (0.0%)	31 (22.0%)	0 (0.0%)
Decreased appetite	27 (32.9%)	1 (1.2%)	33 (40.2%)	2 (2.2%)
Diarrhoea	25 (28.1%)	3 (3.7%)	42 (42.7%)	6 (6.1%)
Neutropenia	23 (28.0%)	20 (18.3%)	26 (24.4%)	22 (20.7%)
Mucosal inflammation	23 (28.0%)	1 (0.0%)	29 (20.7%)	2 (1.2%)
Injection site reaction	19 (23.2%)	0 (0.0%)	21 (25.6%)	0 (0.0%)
Anaemia	11 (13.4%)	3 (3.7%)	33 (45.1%)	20 (28.0%)
Constipation	11 (13.4%)	0 (0.0%)	34 (41.5)	1 (1.2%)
Dysgeusia	10 (12.2%)	0 (0.0%)	10 (11.0%)	0 (0.0%)
Dry mouth	9 (11.0%)	1 (1.2%)	14 (17.0%)	1 (1.2%)

Source: ae-clindb-cut-off-30nov2013, *: PT=MedDRA Preferred Term, **: Pts=patients

SAEs, Related to Belinostat, Reported in ≥ 2 Patients in Group II – Belinostat IV in Combination w/Anthracycline (N=82)

No. of Cases in 82 Patients	MedDRA Preferred Term	CTCAE Grade	MedDRA SOC
3	Febrile neutropenia	Grade 4: 3 events	Blood and lymphatic system disorders
3	Neutropenia	Grade 4: 3 events	Blood and lymphatic system disorders
2	Febrile bone marrow aplasia	Grade 5: 1 event Grade 4: 1 event	Blood and lymphatic system disorders
2	Sepsis	Grade 5: 2 events	Infections and infestations
2	Tumour lysis syndrome	Grade 3: 2 events	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

Source: sae-pvdb-cut-off-30nov2013

AEs with a Frequency ≥ 10% (≥ 4 patients) in Group III – Belinostat IV in Combination with 5-FU

	Total Study Population, N=35			
	AEs Related to Study Drug	AEs Related to Study Drug	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse Event (MedDRA PT*)	No Pts** (%)	No Pts** (%)	No Pts** (%)	No Pts** (%)
Nausea	24 (68.6%)	0 (0.0%)	26 (74.3%)	0 (0.0%)
Fatigue	23 (65.7%)	2 (5.7%)	28 (80.0%)	6 (17.1%)
Vomiting	21 (60.0%)	1 (2.9%)	22 (62.9%)	1 (2.9%)
Anaemia	10 (28.6%)	0 (0.0%)	11 (31.4%)	1 (2.9%)
Anorexia	10 (28.6%)	0 (0.0%)	15 (42.9%)	0 (0.0%)
Dysgeusia	9 (25.7%)	0 (0.0%)	11 (31.4%)	0 (0.0%)
Diarrhoea	8 (22.9%)	0 (0.0%)	12 (34.3%)	0 (0.0%)
Constipation	4 (11.4%)	0 (0.0%)	15 (42.9%)	0 (0.0%)
Dyspnoea	4 (11.4%)	0 (0.0%)	10 (28.6%)	0 (0.0%)

Source: ae-clindb-cut-off-30nov2013 *: PT=MedDRA Preferred Term, **: Pts=patients

Only one SAE (gr. 3 fatigue) was assessed as possibly related to drug in Group III (Belinostat IV w/5-FU)..

AEs with a Frequency ≥ 10% (≥ 15 Patients) in Group IV – Belinostat IV in Combination w/Paclitaxel and/or Carboplatin - Excluding CLN-17 Comparator Arm (N=145)

	Total Study Population, N= 145			
	AEs Related to Study Drug	AEs Related to Study Drug	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse Event (PT*)	No Pts**(%)	No Pts**(%)	No Pts**(%)	No Pts**(%)
Nausea	115 (79.3%)	14 (9.7%)	124 (85.5%)	16 (11.0%)
Fatigue	92 (63.4%)	17 (11.7%)	120 (82.8%)	23 (15.8%)
Vomiting	81 (55.7%)	12 (8.3%)	91 (62.8%)	14 (9.7%)
Alopecia	64 (44.3%)	2 (1.3%)	92 (63.4%)	2 (1.3%)
Diarrhoea	54 (37.2%)	5 (3.4%)	88 (60.7%)	8 (5.5%)
Peripheral sensory neuropathy	38 (26.2%)	5 (3.4%)	69 (47.6%)	5 (3.5%)
Arthralgia	36 (24.8%)	7 (4.8%)	52 (35.9%)	9 (6.2%)
Neutropenia	35 (24.1%)	25 (17.2%)	43 (29.7%)	30 (20.7%)
Flushing	34 (23.4%)	0 (0%)	49 (33.8%)	0 (0%)
Haemoglobin decreased	29 (20.0%)	1 (0.7%)	38 (26.2%)	2 (1.3%)
Thrombocytopenia	28 (19.3%)	13 (9.0%)	34 (23.4%)	17 (11.7%)
Myalgia	28 (19.3%)	7 (4.8%)	37 (25.5%)	7 (4.8%)
Anaemia	28 (19.3%)	4 (2.8%)	54 (37.2%)	10 (6.9%)
Dysgeusia	27 (18.6%)	0 (0%)	37 (25.2%)	0 (0%)
Constipation	25 (17.2%)	0 (0%)	91 (62.8%)	3 (2.1%)
Anorexia	23 (15.7%)	4 (2.8%)	38 (26.2%)	8 (5.5%)
Decreased appetite	21 (14.5%)	1 (0.7%)	34 (23.4%)	1 (0.7%)
Headache	19 (13.1%)	0 (0%)	50 (34.5%)	1 (0.7%)
Rash	18 (12.4%)	3 (2.1%)	33 (22.8%)	3 (2.1%)
Neuropathy peripheral	17 (11.7%)	1 (0.7%)	22 (15.2%)	2 (1.3%)
Dehydration	15 (10.0%)	5 (3.4%)	27 (18.6%)	8 (5.5%)
Platelet count decreased	15 (10.0%)	3 (2.1%)	15 (10.0%)	3 (2.1%)
Dizziness	15 (10.0%)	1 (0.7%)	42 (30.0%)	1 (0.7%)

Source: as-clindb-cut-off-30nov2013 *: PT=MedDRA Preferred Term, **: Pts=patients

SAEs, Related to Belinostat, Reported in ≥ 2 Patients in Group IV – Belinostat IV in Combination w/ Paclitaxel and/or Carboplatin (Excluding CLN-17 Comparator Arm) (N=145)

No. of Cases in 145 Patients	MedDRA Preferred Term	CTCAE Grade	MedDRA SOC
6	Vomiting	Grade 3: 5 events Grade 2: 1 event	Gastrointestinal disorders
3	Dehydration	Grade 3: 2 events Grade 2: 1 event	Metabolism and nutrition disorders
2	Hypersensitivity	Grade 3: 2 events	Immune system disorders
2	Nausea	Grade 3: 1 event Grade 2: 1 event	Gastrointestinal disorders

Source: sae-pvdb-cut-off-30nov2013

AEs Reported in ≥ 2 Patients in Group V–Belinostat IV in Combination with Bortezomib

	Total Study Population, N=7			
	AEs Related to Study Drug	AEs Related to Study Drug	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse Event (MedDRA PT*)	No Pts (%)	No Pts (%)	No Pts (%)	No Pts (%)
Fatigue	3 (42.9%)	0 (0.0%)	6 (85.7%)	0 (0.0%)
Anaemia	2 (28.6%)	1 (14.3%)	5 (71.4%)	2 (28.6%)
Blood creatinine increased	2 (28.6%)	2 (28.6%)	3 (42.9%)	2 (28.6%)
Chills	2 (28.6%)	0 (0.0%)	2 (28.6%)	0 (0.0%)
Hypocalcaemia	2 (28.6%)	1 (14.3%)	2 (28.6%)	1 (14.3%)
Nausea	2 (28.6%)	0 (0.0%)	3 (42.9%)	0 (0.0%)
Pyrexia	2 (28.6%)	0 (0.0%)	4 (57.1%)	0 (0.0%)
Renal failure acute	2 (28.6%)	2 (28.6%)	2 (28.6%)	2 (28.6%)

Source: ae-clindb-cut-off-30nov2013, *: PT=MedDRA Preferred Term, **: Pts=patients

Related SAEs Reported in ≥ 2 Patients in Group V – Belinostat in Combination w/Bortezomib (N=7)

No. of Cases in 7 Patients	MedDRA Preferred Term	CTCAE Grade	MedDRA SOC
2	Renal failure acute	Grade 4: 1 event Grade 3: 1 event	Renal and urinary disorders

Source: sae-pvdb-cut-off-30nov2013

Safety in Group VI - Belinostat IV in Combination w/CHOP (N=3). Only 5 AEs (all in 1 patient) were assessed as related to study drug. No SAEs were assessed as related to study drug.

AEs with a Frequency ≥ 10% (≥ 12 Patients) in Group VII – Belinostat Oral Monotherapy

	Total Study Population, N=120			
	AEs Related to Belinostat	AEs Related to Belinostat	All AEs	All AEs
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥3
Adverse Event (MedDRA PT*)	No Pts (%)	No Pts (%)	No Pts (%)	No Pts (%)
Fatigue	72 (60.0%)	14 (11.7%)	97 (80.8%)	18 (15.0%)
Nausea	71 (59.2%)	2 (1.7%)	82 (68.3%)	2 (1.7%)
Diarrhoea	55 (45.8%)	12 (10.0%)	74 (61.7%)	14 (11.7%)
Anorexia	48 (40.0%)	1 (0.8%)	63 (52.5%)	2 (1.7%)
Vomiting	48 (40.0%)	2 (1.7%)	63 (52.5%)	2 (1.7%)
Blood creatinine increased	25 (20.8%)	1 (0.8%)	33 (27.5%)	1 (0.8%)
Weight decreased	23 (19.2%)	0 (0.0%)	36 (30.0%)	0 (0.0%)
Constipation	19 (15.8%)	0 (0.0%)	52 (43.3%)	3 (2.5%)
Dry mouth	19 (15.8%)	0 (0.0%)	43 (35.8%)	0 (0.0%)
Dysgeusia	19 (15.8%)	0 (0.0%)	27 (22.5%)	0 (0.0%)
Thrombocytopenia	18 (15.0%)	8 (6.7%)	22 (18.3%)	8 (6.7%)
Dehydration	16 (13.3%)	2 (1.7%)	21 (17.5%)	4 (3.3%)
Dizziness	16 (13.3%)	0 (0.0%)	25 (20.8%)	0 (0.0%)
Decreased appetite	13 (10.8%)	0 (0.0%)	19 (15.8%)	0 (0.0%)

Source: IB Version 9.0, Table 34, 03-May-2012. *: PT=MedDRA Preferred Term, **: Pts=patients

SAEs, Related to Belinostat, in ≥ 2 Patients in Group VII - Oral Belinostat Monotherapy Study (N=120)

No. of Cases in 120 Patients	MedDRA Preferred Term	CTCAE Grade	MedDRA SOC
5	Fatigue	Grade 3: 5 events	General disorders and administration site conditions
3	Vomiting	Grade 3: 1 event Grade 2: 2 events	Gastrointestinal disorders
3	Pyrexia	Grade 1: 3 events	General disorders and administration site conditions
2	Diarrhoea	Grade 3: 1 event Grade 2: 1 event	Gastrointestinal disorders
2	Blood creatinine increased	Grade 3: 1 event Grade 2: 1 event	Investigations
2	Lipase increased	Grade 4: 1 event Grade 3: 1 event	Investigations
2	Dehydration	Grade 3: 1 event Grade 2: 1 event	Metabolism and nutrition disorders
2	Hyponatraemia	Grade 3: 2 events	Metabolism and nutrition disorders

Source: IB Version 9.0, Table 35, 03-May-2012

Expected Serious Adverse Events Related to Belinostat (Observed in ≥ 2 Patients)

System Organ Class/ Preferred Term	CTCAE*	Comment**
Blood and lymphatic system disorders		
Anaemia	Grade 4	
Febrile bone marrow aplasia	Grade 5	Combination therapy only (Anthracycline)
Febrile neutropenia	Grade 4	Grade 4 has only occurred in combination therapy (Anthracycline). Grade 3 also reported in monotherapy.
Neutropenia	Grade 4	Combination therapy only (Anthracycline and Carboplatin/Paclitaxel).
Thrombocytopenia, Platelet count decreased	Grade 4	
Cardiac disorders		
Atrial fibrillation	Grade 3	
Electrocardiogram QT prolonged*	Grade 3	Combination therapy only (Anthracycline and Carboplatin/Paclitaxel)
Electrocardiogram T wave inversion	Grade 1	Combination therapy (Carboplatin/Paclitaxel) and oral formulation only
Gastrointestinal disorders		
Constipation	Grade 3	
Diarrhea	Grade 3	
Nausea	Grade 3	
Vomiting	Grade 3	
General disorders and administration site conditions		
Fatigue	Grade 3	
Pyrexia	Grade 2	
Immune system disorders		
Hypersensitivity	Grade 3	Grade 3 has only occurred in combination therapy (Anthracycline and Carboplatin/Paclitaxel). Grade 2 also reported in monotherapy.
Infections and infestations		
Infection	Grade 3	
Neutropenic sepsis	Grade 4	Combination therapy only (Anthracycline and Carboplatin/Paclitaxel)
Pneumonia	Grade 3	
Sepsis	Grade 5	Grade 5 has only occurred in combination therapy (Anthracycline), and oral formulation. Grade 3 also reported in monotheraphy.
Investigations		
Lipase increased	Grade 4	Oral formulation only
Transaminases increased (including alanine/aspartate aminotransferase increased)	Grade 4	

System Organ Class/ Preferred Term	CTCAE*	Comment**
Metabolism and nutrition disorders		
Dehydration	Grade 3	
Hyponatraemia	Grade 3	Oral formulation only
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)		
Tumor lysis syndrome	Grade 3	Combination therapy only (Anthracycline)
Renal and urinary disorders		
Azotemia	Grade 4	
Blood creatinine increased *	Grade 3	Grade 3 has only occurred in oral formulation. Grade 2 also reported in monotherapy.
Renal failure acute	Grade 4	Grade 4 in combination therapy only (Bortezomib). Grade 3 also reported in oral monotherapy
Respiratory, thoracic and mediastinal disorders		
Pneumonitis / Alveolitis	Grade 3	
Skin and subcutaneous tissue disorders		
Rash	Grade 3	Grade 3 has only occurred in combination therapy (Anthracycline). Grade 2 also reported in monotherapy.
Vascular disorders		
Deep vein thrombosis	Grade 3	
Hypotension	Grade 3	Grade 3 has only occurred in combination therapy (Carboplatin/Paclitaxel). Grade 2 also reported in oral formulation.
Vasculitis	Grade 3	

* CTCAE grading includes all smaller values of CTCAE grading. Thus if Grade 3 is listed, events of Grade 1-3 will be considered expected.

*: Belongs to SOC Investigations. **: IV formulation if nothing else is mentioned

Source: Related SAEs PV DB cut-off 30nov2013

5.1.19 Availability: Belinostat is an investigational agent supplied to investigators by Spectrum Pharmaceuticals.

5.1.20 Agent Ordering: Belinostat may be requested by the Principal Investigator (or their authorized designee) at each participating institution after patient assignment to cohort 2. The research pharmacy at each respective institution will prepare each treatment dose of belinostat for enrolled patients and transfer to the study team/infusion center for intravenous administration to patients

5.1.21 Agent Accountability: The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all investigational product.

5.1.22 Summary of Background: Belinostat, also known as PXD101, is a pan HDAC inhibitor, inhibiting both Class I and Class II HDAC isoforms with a nanomolar potency. It is a low molecular weight HDAC inhibitor with a sulfonamide-hydroxamidestructure. The chemical name of belinostat is N-hydroxy-3-[3-(phenylsulfamoyl) phenyl] prop-2-enamide. The hydroxamate region of belinostat chelates a zinc ion, which is necessary for activity of the histone deacetylase family of enzymes. Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anticancer therapeutics. Several HDAC inhibitors from multiple chemical classes have been developed and are currently in clinical trials. Trichostatin and butyric acid were among the first HDAC inhibitors to be administered to patients, but these were found to be clinically unsuitable due to potency and formulation issues [33, 34]. Depsipeptide was

originally selected for clinical study based on its antiproliferative effects; subsequently it was discovered to antagonize HDACs and was the first HDAC inhibitor to demonstrate clinical efficacy [35]. Among HDAC inhibitors currently in clinical trials, belinostat is one of the most potent with activity in the nanomolar range. Although most evaluation of this drug has been with an IV formulation to date, this inhibitor does show good oral bioavailability and future development for use in brain tumors or other indications may proceed in this direction.

5.1.23 Mechanism of Action: The HDACs exert their targeted action during post-translational acetylation of core nucleosomal histones, which affects chromatin structure, thereby regulating gene expression. DNA that is wrapped around condensed, non-acetylated histones is transcriptionally inactive, whereas acetylation of N-terminal histone lysine residues exposes DNA to important transcription factors that promote transcriptional activity [36, 37]. The dynamic equilibrium between histone acetylation and deacetylation is regulated by histone acetyltransferases (HATs) and HDACs. The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis [38]. The effects of HDACs are not limited to histone deacetylation. HDACs also act as members of a protein complex to recruit transcription factors to the promoter region of genes, including those of tumor suppressors, and they affect the acetylation status of specific cell cycle regulatory proteins [36].

5.1.24 Non-Clinical Activity: Belinostat is a novel and potent pan-HDAC inhibitor which has been shown to alter the acetylation status of histone and non-histone proteins in cancer cells. Nonclinical *in vitro* studies have demonstrated that belinostat inhibits the growth of cell lines representing a wide range of cancer types with sub to low µM IC_{50} potency (see Investigator's Brochure, Ver. No. 11.0, [39, 40]) and is active on cancer cells that have developed resistance to other chemotherapeutics [41]. Belinostat has also demonstrated tumor growth inhibitory activity in a variety of animal models of cancer [4, 41-43]. Mechanistically, belinostat and HDAC inhibitors in general induce an increase in acetylation of both histone and non-histone proteins resulting in less compact chromatin structure, cell cycle arrest, apoptosis, and a decrease in tumor cell proliferation studies [4, 41, 43, 44].

5.1.25 Belinostat (PXD101) Combination Studies: Accumulating evidence has demonstrated the effectiveness of HDAC inhibitors in combination with several other agents in vitro. Vorinostat, an alternative HDAC inhibitor, in combination with a variety of drugs including DNA hypomethylating agents such as 5-azacytidine or decitabine, other chemotherapies such as 5-fluorouracil, etoposide, doxorubicin, cisplatin, taxotere, or gemcitabine and targeted agents such as imatinib, trastuzumab, or bortezomib appear to have increased anti-neoplastic activity [25, 45-49]. In addition to single agent activity, belinostat has also demonstrated synergistic activity *in vitro* and beneficial effect *in vivo* when used in combination with a large number of antineoplastic drugs (e.g., 5-FU, carboplatin, paclitaxel, bortezomib, docetaxel, erlotinib, trabectedin, sorafenib) [41, 43, 50-55].

5.1.26 Preclinical Studies of HDAC Inhibition in Malignant Gliomas: HDAC inhibitors such as belinostat induce cell cycle alterations (such as activation of checkpoints and G2/M

cell cycle arrest) and apoptosis in malignant cells in vitro. The ability of HDAC inhibitors to alter nucleosome structure and chromatin conformation suggests that they may have the capacity to modulate sensitivity to chemotherapeutic agents, in particular, those that target DNA such as alkylating agents. Recent work demonstrates that pretreatment of tumor cell lines in vitro with histone deacetylase inhibitors may sensitize cells to various chemotherapeutic agents or radiation [24, 25]. Using specific glioma systems, intracranial administration of vorinostat in an orthotopic glioma mouse model increased survival time from 22 days to 42 days [56]. For short-term studies, histological analysis showed an 80% reduction of tumor volume in the vorinostat treated group. This reduction in tumor volume was associated with a significant increase in the apoptosis rate and a decrease in proliferation and angiogenesis [56]. Another in vivo murine study suggested that vorinostat (10 mg/kg, i.v., or 100 mg/kg, i.p.) could cross the blood-brain barrier as shown by significantly increased levels of acetyl-H3 and acetyl-H4 in the brain tissue. Furthermore, the drug significantly ($P<0.05$) inhibited the proliferation of GL26 glioma cells growing in the brains of mice and increased their survival [57]. Eyupoglu et al. [58] reported that in vivo, a single intratumoural injection of vorinostat 7 days after orthotopic implantation of glioma cells in syngeneic rats doubled their survival time. Additional work specifically in human glioma cell lines indicate the effectiveness of HDAC inhibition for growth inhibition either as monotherapy or in combination with other agents [59-62]. These observations support HDAC inhibition as a possible and promising pharmacotherapy for malignant gliomas. While no published study have demonstrated preclinical efficacy of belinostat in glioma tumor models, this drug has been tested in a orthotopic nude rat model involving intracranial injection of U87MG glioma cells and found to have efficacy that surpassed what was previously seen with vorinostat in this same model [29]. This result coupled with previous work using other HDAC inhibitors in glioma models and the known ability of belinostat to cross the blood-brain barrier [5] provides a good rationale to further pursue testing of this drug in glioblastomas.

5.1.27 Clinical Trial Experience: Belinostat is FDA approved for use in patients with relapsed/refractory peripheral T-cell lymphoma with recommended dosing administered IV at 1000 mg/m^2 1x/day on days 1-5 every three weeks. Phase I evaluation using belinostat as monotherapy found 1000 mg/m^2 (IV daily on days 1-5 every 3 weeks) to be the maximal tolerated dose (MTD) with 3 of 5 patients receiving 1200 mg/m2 developing a dose limiting toxicity (DLT) [63]. Of note, histone H4 hyperacetylation was observed after each infusion and was sustained for 4-24 hours in a dose dependent fashion. Belinostat has also been tested in combination with other chemotherapeutic agents. Phase 1 evaluation using belinostat in combination with either paclitaxel and/or carboplatin found no DLTs with dosing up to 1000 mg/m^2 (IV daily on days 1-5 every 3 weeks) [64]. Similarly, additional evaluation on a phase I/II study where belinostat was dosed with cisplatin, doxorubicin and cyclophosphamide found excellent tolerance (no DLTs) in patients treated with 1000 mg/m^2 (IV daily on days 1-5 every 3 weeks) [65]. Oral dosing of belinostat has also been evaluated on a company-sponsored CLN-9 phase I study with MTD being defined at different levels depending on the dosing schedule (250 mg qday; 750 mg/day on days 1-14 q3weeks; 2000 mg/day on days 1-5 q3weeks) (see Investigator's Brochure, ver. 11.0, 23-May-2014). Overall, belinostat has been used in 457 patients on 14 NCI-

sponsored and 693 patients on 17 company-sponsored clinical trials with toxicitiy results presented earlier in the toxicity section (**5.1.18. Adverse Events and Potential Risks for Belinostat)**.

To date, belinostat has not been tested in combination with radiation or temozolomide. However, the HDAC inhibitor vorinostat has been tested in conjunction with both radiation and temozolomide with good tolerance of therapy. The NCCTG/ABTC phase II trial for use of vorinostat in newly diagnosed glioblastoma patients dosed vorinostat at the 300 mg/day given 5 of 7 days (take on M-F, break on Sa-Su) during the 6 week course of RT/TMZ followed by 4 week break and then vorinostat 400 mg/day given on days 1-7 and 15-21 out of each 28 day cycle (TMZ is given on days 1-5) for 12 cycles or until progression. Given this experience and the fact that belinostat is extremely well-tolerated with a variety of other chemotherapies, we expect patients to tolerate the concurrent administration of belinostat with RT/TMZ well. Our plan is to enroll an initial small cohort of patients to either confirm good tolerance with RT/TMZ at the recommended monotherapy dose (1000 mg/m2 1x/day on days 1-5 q3weeks) or a lower dose (if full dose is not tolerated) before expanding enrollment at the identified MTD.

5.2 Temozolomide (NSC# 362856)

5.2.1 Chemical Name: 3.4-Dihydro-3-methyl-4-oxoimidazo-[5,1-d]-1,2,3,5-tetrazin-8-carboxamide. (Former name includes 8 carbamoyl-3-methylimidazo-5,1-d] 1.2.3.5-tetrazin-4-(3H)-one.

5.2.2 Other Names: Temodar

5.2.3 Mechanism of Action: Temozolomide is not directly active but undergoes rapid non-enzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O6 and N7 positions at guanine.

5.2.4 Pharmacokinetics: Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and Tmax increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast. Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

5.2.5 Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively. Approximately 38% of the administered temozolomide total radioactive

dose is recovered over 7 days: 37% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is ~5.5 L/hr/m.

5.2.6 Preclinical Studies: The pharmacokinetics of temozolomide were evaluated in several studies conducted by Schering-Plough Research Institute (SPRI) using either male and female rats or male and female dogs following intravenous (IV) and/or oral single dose administration (Investigational Brochure –Temozolomide. Schering Plough). Plasma concentrations of temozolomide were also monitored during single-cycle, three-cycle and six-cycle studies in rats and dogs to evaluate exposure of these species to toxicological doses of temozolomide (Investigational Brochure-Temozolomide, Schering Plough). In a single dose pharmacokinetic rat study, fasting male and female rats received 200 mg/m2 temozolomide either intravenously or orally. Blood, urine and brain tissues were collected through 48 hours post dose. Absolute oral bioavailability based on the oral/intravenous ratio of area under the plasma concentration-time curve from time zero to infinity [AUC(I)] for temozolomide was 96% to 100%. Temozolomide was rapidly eliminated from the plasma, with a terminal plasma half-life of approximately 1.2 hours after IV or oral administration. Temozolomide penetrated rapidly into brain, and the extent of drug penetration ranged between 35% and 39% based on the brain to plasma ratio for AUC (I). No sex-related differences were noted in either the plasma or brain pharmacokinetic parameters. Similar results were demonstrated in dogs. There has been no evidence of temozolomide accumulation in multiple dosing studies of rats and dogs (Investigational Brochure-Temozolomide, Schering Plough).

5.2.7 Pharmaceutical Data: Temozolomide (Temodar®) is supplied in white, opaque, preservative free, 2-piece, hard gelatin capsules in the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, and 250 mg. Capsules should not be opened or chewed. If capsules are accidentally opened or damaged, inhalation or contact with the skin should be avoided. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lautyl sulfate NF.

5.2.8 Storage and Stability: Temozolomide should be stored at room temperature. The capsules are packaged in 30 cc 28 mm-48-Type I amber glass bottles (30 capsules/bottle) and should be stored between 2 and 30 degrees Centigrade. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.

5.2.9 Route of Administration: Temozolomide should be taken by mouth after fasting from solid food for 2 hours.

5.2.10 Drug Source: Temozolomide has been approved by the FDA for refractory anaplastic astrocytomas and newly-diagnosed glioblastoma. Patients or third party payers must pay for the Temozolomide. If the patient is unable to pay for the drug, he/she may seek assistance through Schering-Plough Pharmaceutical's Commitment to Care Program.

5.2.11 Adverse Reactions: The most common reactions to temozolomide include nausea, vomiting, headache, fatigue and hematologic effects. These events are usually mild to moderate. Nausea and vomiting is usually readily controlled with antiemetics. Myelosuppression (thrombocytopenia and neutropenia) is the dose-limiting side effect. It usually occurs within the first few cycles of therapy and is not cumulative. In prior studies, myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. Other less common side effects may include somnolence or insomnia, anorexia, constipation, diarrhea, weight loss, abdominal pain, rash, pruritis, anxiety, depression, pain when swallowing, hyperglycemia, epistaxis, empyema, pulmonary edema, respiratory insufficiency, respiratory arrest, cardiac arrest, toxic hepatitis, liver or kidney abnormalities and/or breast tumors.

The information provided in the consent includes the following:

Likely side effects:

- Nausea and vomiting, especially on the first day of each cycle. It may be necessary to use medication to prevent this.
- Constipation
- Loss of appetite
- Lowering of your blood counts, which may result in low white blood cells, platelets, and red blood cells. If you have very low white blood cells, you are at a higher risk for infections. Lung infections have occurred in patients receiving daily treatment with temozolomide combined with radiation and steroids (e.g., dexamethasone). To prevent this, your doctor may ask you to take preventative medication during this time. Apart from this, if you develop fever it may be necessary to treat you with antibiotics. Low platelets may result in a bleeding tendency, if necessary this can be treated with platelet transfusions. Low red blood cells can also be treated with transfusions.
- Fatigue, lethargy, insomnia, weakness
- Headache
- Hair loss and rash

Less Likely side effects:

- Kidney problems and high blood sugar
- Abnormal liver tests and diarrhea
- Recently, cases of hepatic injury, including fatal hepatic failure, have been observed in patients enrolled in clinical studies utilizing the agent temozolomide. In addition, it was noted that liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation. Refer to the package insert for additional information on adverse events observed to date.

A tabular summary of side effects follows:

	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TNZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3

Subjects Reporting any Adverse Reaction	**258**	**(91)**	**74**	**(26)**	**266**	**(92)**	**80**	**(28)**	**206**	**(92)**	**82**	**(37)**
Body as a Whole - General Disorders												
Anorexia	25	(9)	1	(< 1)	56	(19)	2	(1)	61	(27)	3	(1)
Dizziness	10	(4)	0		12	(4)	2	(1)	12	(5)	0	
Fatigue	139	(49)	15	(5)	156	(54)	19	(7)	137	(61)	20	(9)
Headache	49	(17)	11	(4)	56	(19)	5	(2)	51	(23)	9	(4)
Weakness	9	(3)	3	(1)	10	(3)	5	(2)	16	(7)	4	(2)
Central and Peripheral Nervous System Disorders												
Confusion	12	(4)	6	(2)	11	(4)	4	(1)	12	(5)	4	(2)
Convulsions	20	(7)	9	(3)	17	(6)	10	(3)	25	(11)	7	(3)
Memory Impairment	12	(4)	1	(< 1)	8	(3)	1	(< 1)	16	(7)	2	(1)
Disorders of the Eye												
Vision Blurred	25	(9)	4	(1)	26	(9)	2	(1)	17	(8)	0	
Disorders of the Immune System												
Allergic Reaction	7	(2)	1	(< 1)	13	(5)	0		6	(3)	0	
Gastrointestinal System Disorders												
Abdominal Pain	2	(1)	0		7	(2)	1	(< 1)	11	(5)	1	(< 1)
Constipation	18	(6)	0		53	(18)	3	(1)	49	(22)	0	
Diarrhea	9	(3)	0		18	(6)	0		23	(10)	2	(1)
Nausea	45	(16)	1	(< 1)	105	(36)	2	(1)	110	(49)	3	(1)
Stomatitis	14	(5)	1	(< 1)	19	(7)	0		20	(9)	3	(1)
Vomiting	16	(6)	1	(< 1)	57	(20)	1	(< 1)	66	(29)	4	(2)
Injury and Poisoning												
Radiation Injury NOS	11	(4)	1	(< 1)	20	(7)	0		5	(2)	0	
Musculoskeletal System Disorders												
Arthralgia	2	(1)	0		7	(2)	1	(< 1)	14	(6)	0	
Platelet, Bleeding and Clotting Disorders	3	(1)	0		11	(4)	8	(3)	19	(8)	8	(4)
Thrombocytopenia Psychiatric Disorders												

Insomnia	9	(3)	1	(< 1)	14	(5)	0		9	(4)	0	
Respiratory System Disorders												
Coughing	3	(1)	0		15	(5)	2	(1)	19	(8)	1	(< 1)
Dyspnea	9	(3)	4	(1)	11	(4)	5	(2)	12	(5)	1	(< 1)
Skin and Subcutaneous Tissue Disorders												
Alopecia	179	(63)	0		199	(69)	0		124	(55)	0	
Dry Skin	6	(2)	0		7	(2)	0		11	(5)	1	(< 1)
Erythema	15	(5)	0		14	(5)	0		2	(1)	0	
Pruritus	4	(1)	0		11	(4)	0		11	(5)	0	
Rash	42	(15)	0		56	(19)	3	(1)	29	(13)	3	(1)
Special Senses Other, Disorders												
Taste Perversion	6	(2)	0		18	(6)	0		11	(5)	0	

*One patient who was randomized to RT only arm received RT+temozolomide.
RT+TMZ=radiotherapy plus temozolomide; NOS=not otherwise specified.
Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥ 3 column.

Source: http://www.rxlist.com/temodar-drug.htm

Please refer to the package insert for additional information.

5.2.12 Summary of Background: Temozolomide (TMZ, Temodar®) is an orally administered alkylating agent with activity against malignant gliomas. It is a prodrug that spontaneously converts at physiologic pH to the active alkylating agent 5-(3-methyltriazen-1-yl)imidazole-4-carboximide (MTIC) under physiologic conditions. The cytotoxicity of temozolomide is principally mediated through methylation of DNA at the O6 position of guanine (Investigational Brochure-Temozolomide).

5.2.13 Effects of Temozolomide on Glioma Cells: The alkylating agents temozolomide and BCNU are mainstays of adjuvant therapy for malignant glioma. Temozolomide functions primarily as an alkylating agent inducing methylation of the O-6 residues of guanine, generating mismatch pairing and leading to futile DNA mismatch repair possibly with strand breaks [66]. The biologic consequences of these molecular effects of the agent include alterations in the cell cycle kinetics and induction of apoptosis. These effects have been demonstrated in a variety of malignant cells particularly in hematopoietic malignancies in vitro and are believed to be the mechanisms of action of the agent in humans as well. Studies focusing on the effects of this agent against gliomas are fewer but have shown that mechanisms similar to those for hematogenous malignancies are operative in this tumor type as well. The cell cycle changes induced by temozolomide are of particular relevance to the rationale for this trial proposal. In vitro studies have shown that temozolomide induces a prolonged G2/M arrest associated with an increase in p53 and p21 protein levels [67]. The cells showed decreased proliferation by a clonogenic assay and

exhibited features of senescence in cells with wild type p53; in cells with deficient p53, a transient G2/M arrest was followed by induction of apoptosis possibly by mitotic catastrophe. The induction of G2/M arrest in glioma cells has been associated with Chk1 activation and inhibitory phosphorylation of cdc25c and cdc2 inactivating the cyclin B1/cdc2 complex necessary for progression of the cell cycle from G2 to M phase. [67]. Pharmacologic inhibition of Chk1 or of the p38MAPK pathways sensitized glioma cells to temozolomide-induced apoptosis. These data suggest the biologic effects of temozolomide are related to the cell cycle changes and apoptosis induced by this agent.

5.2.14 Preclinical Studies With Temozolomide: Following IV and oral administration (Investigator's Brochure -Temozolomide. Schering Plough), plasma concentration of temozolomide was also monitored during single-cycle, three-cycle, and six-cycle studies in rats and dogs to evaluate exposure of these species to toxicologic doses of temozolomide. Data from the single-dose pharmacokinetic rat study indicated a high bioavailability in the range of 96% to 100%. Temozolomide was rapidly eliminated from the plasma, with a terminal half-life of ~1.2 hours after IV or oral administration. Temozolomide penetrated rapidly into brain, and the extent of drug penetration into brain ranged from 35% to 39% based on the brain to plasma AUC (I) (Investigator's Brochure -Temozolomide. Schering Plough). Brain concentrations of temozolomide declined rapidly, with a terminal phase half-life (1.1 to 1.3 hr) similar to that of plasma. Based on the CSF to plasma ratio for the area under the plasma concentration–time curve from time 0 to last measurable concentration (AUC(tf)), the penetration of temozolomide and 14C-temozolomide into rat CSF ranged from 41% to 44%, respectively. Brain concentrations of radioactivity and temozolomide declined rapidly, thereafter. Results from the single-cycle and three-cycle toxicity studies in rats and dogs (5 days of consecutive dosing during each cycle) revealed dose-related and sex-independent plasma concentrations of temozolomide on Days 1 and 5. There was no temozolomide accumulation in either rats or dogs upon multiple dosing (Investigator's Brochure -Temozolomide. Schering Plough).

5.2.15 Temozolomide Clinical Experience:

5.2.15.1 Adult Phase I/II Studies of Temozolomide: As a result of the encouraging preclinical data, a phase I trial with temozolomide was conducted by the Cancer Research Campaign (CRC) Phase I-II Clinical Trials Unit in the United Kingdom (UK). This trial was conducted in two phases. The first 51 patients were treated with temozolomide administered either orally or intravenously, using a single-dose schedule. The subsequent 133 patients received a 5-day oral schedule. Cycles of temozolomide were repeated every 28 days. The total doses administered over 5 days were 750, 900, 1000, and 1200 mg/m2. Dose-limiting toxicity was myelosuppression and the maximum tolerated dose (MTD) was defined at 1000 mg/m2. Only one course was administered at 1200 mg/m2 and resulted in Grade 4 myelotoxicity. The nadir for hematologic parameters of neutropenia or thrombocytopenia usually occurred at 21 days or later following the first dose of each cycle with recovery to at least Grade 1 by 28 days. Overall, Grades 1 to 4 anemia, leukopenia and thrombocytopenia occurred in 17%, 12% and 9% of the evaluable courses, respectively. Grade 3 and 4

thrombocytopenia and leukopenia occurred in 4% and 3% of the evaluable courses, respectively, and were primarily seen at doses >1000 mg/m2. Mild to moderate (Grades 1 and 2) nausea and vomiting were reported in 28% of the evaluable courses at doses up to 750 mg/m2, inclusive. These events were usually limited to day 1 and were readily controlled with standard antiemetics. At higher doses (>750-1200 mg/m2), Grades 3 and 4 nausea and vomiting were seen in 9% of the evaluable courses. The percentages of adverse events reported included: constipation (10%), headache (5%), rash (4%), renal disorders (3%), elevated hepatic enzymes (3%), alopecia (2%), diarrhea (2%), itching and burning (<1%), lethargy (<1%), altered consciousness (<1%), and esophagitis (<1%).

Based on this study, the recommended starting dose of temozolomide for Phase II trials was 150 mg/m2/day, orally, once a day for 5 days (total dose 750 mg/m2) for the first cycle with subsequent dose escalation to 200 mg/m2/day, once a day for 5 days (total dose 1000 mg/m2) in the absence of myelotoxicity. The CRC subsequently conducted three Phase II trials of temozolomide in patients with documented progression who had either high-grade glioma, advanced malignant melanoma, or low-grade non-Hodgkin's lymphoma (Investigator's Brochure -Temozolomide. Schering Plough) [68]. Activity in these tumor types was reported in all three studies.

5.2.15.2 Temozolomide for Recurrent Malignant Gliomas: A randomized trial was conducted to compare the efficacy of temozolomide with procarbazine in patients with GBM at first relapse [69]. Patients were randomized to temozolomide administered orally once daily for 5 days at a starting dose of either 200 mg/m2/day (no prior chemotherapy) or 150 mg/m2/day (prior chemotherapy) every 28 days, or procarbazine 150 mg/m2/day for 28 days every 56 days. Temozolomide performed better than procarbazine in terms of progression free survival (PFS), overall survival and objective response to treatment, although the differences were modest. The 6-months progression free survival (6M-PFS) was 21% in the temozolomide group compared to 8% in the procarbazine group (p=0.008). In comparison, the 6M-PFS for GBM patients in 8 negative phase II trials from MD Anderson Cancer Center was only 15% (Wong et al, 1999). Median PFS was 2.89 months with temozolomide compared to 1.97 months with procarbazine. The median overall survival for the intent-to-treat population of temozolomide recipients with GBM (7.34 months) was longer than for procarbazine recipients (5.82 months). 5.4% of TMZ patients and 5.3% of procarbazine patients had a PR, while 40.2% of temozolomide patients and 27.4% of procarbazine patients had SD. The overall response rate (PR + SD) was 45.6% in the temozolomide group and 32.7% in the procarbazine group [69]. The most common grade 3 or 4 toxicities in the temozolomide group were headache (10%), thrombocytopenia (7%), neutropenia (4%), fatigue (3%), vomiting (4%) and nausea (4%). Quality of life was significantly better in the temozolomide group.

In another trial, the efficacy of temozolomide for AA at first relapse was evaluated in a phase II study consisting of 162 patients [68]. Temozolomide

was administered once daily for 5 days every 28 days at a starting dose of either 200 mg/m^2/day in patients who had received no prior chemotherapy or 150 mg/m^2/day in patients who had received prior chemotherapy. 8% of patients experienced a CR, 27% had a PR and 26% had SD, producing an overall response rate of 61%. 6M-PFS was 46% compared to 31% from the MD Anderson database of 8 negative phase II trials for recurrent AA [70]. The MTP was 5.4 months and the median survival was 14.6 months. Both overall response and maintenance of progression-free status were associated with health-related quality-of-life benefits, independent of steroid use [71]. Based on these results, temozolomide was approved by the FDA for the treatment of recurrent AA in 1999. Over the past few years TMZ has become the treatment of choice for patients with recurrent malignant gliomas. However, the responses tend to be modest and short-lived. Several different schedules have been evaluated but none have been clearly superior to the standard regimen [72]. There is significant interest in combining temozolomide with other agents to increase its effectiveness.

5.2.15.3 Temozolomide for Newly Diagnosed Glioblastomas: Based on preclinical evidence that temozolomide has additive activity when combined with radiation therapy (RT) [73], Stupp et al., conducted a phase II study in which 64 patients with newly-diagnosed GBM were treated with temozolomide 75 mg/m2/d x 6 weeks with concomitant fractionated RT (60 Gy; 2 Gy x 5d/wk for 6 weeks) followed by temozolomide adjuvant therapy (200 mg/m2/d x 5 days every 28 days for 6 cycles) [74]. This regimen was well-tolerated and the median survival of 16 months was significantly better than the historic median survival of GBM of 9-12 months. As a result of these promising results, the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) conducted a randomized phase III trial (EORTC Study 26981) of 573 patients comparing this regimen of concomitant and adjuvant temozolomide and radiation therapy to radiation therapy alone in patients with newly-diagnosed GBM [1]. This study showed that the combination of temozolomide with radiation therapy was well-tolerated and resulted in a survival benefit. The median survival of patients treated with temozolomide + radiation therapy was increased compared to radiation therapy alone (14.6 mo v.12.1 mo; p< .0001). In addition, patients receiving temozolomide with radiation therapy had a significantly higher percentage of patients surviving at two years (26%) than patients receiving radiation therapy alone (10%). This study conclusively demonstrated for the first time that adjuvant chemotherapy is of benefit in patients with GBM.

6.0 REGISTRATION PROCEDURES

6.1 Patient registration/cohort assignment

6.1.1 Pre-registration: Emory: Pre-registration must be completed and sent to the Central Subject Registrar and to the Office of Clinical Research. After receipt of the pre-registration form and confirmation of a valid, signed informed consent form/HIPAA

authorization form, the Winship Clinical Trials office will assign a patient study number..

Participating site(s): After each subject signs consent, the Central Subject Registration form is to be completed and sent to Winship within 24 hours of consent. This form, along with the valid, signed informed consent form/HIPAA authorization form, is to be faxed or emailed to Winship's Central Subject Registrar per instructions on the form.

6.1.2 Patient study number assignment/confidentiality: Subjects will be assigned a coded designation according to the site at which the subject signs consent. (QINU01, the site initials, and a consecutive number, e.g. 1st patient entered on study at Emory will be assigned QINU01EM001). Actual names, contact information and relationship to this code will be kept in a locked file cabinet in Winship Clinical Trials Office.

6.1.3 Registration: Participating site(s): The Eligibility checklist is to be printed from OnCore and verified by 2 people, of which one must be a clinical investigator or co-investigator. The completed and signed eligibility checklist along with all redacted supporting source documentation must be submitted to the Winship Multi-site Coordinator or designee (fax 404-778-0417) within 14 days after pre-registration but no later than 2 business days from scheduled treatment visit. Eligibility will be confirmed by a clinical principal or co-investigator and the Multi-site Coordinator or designee within 1 business day of receipt of all eligibility documentation and confirmation will be sent to the participating site along with cohort assignment, if subject meets criteria The required tissue sample may be submitted to Dr. Dan Brat, study pathologist at Emory, within 30 days after completing registration. Subject needs to start study intervention $\leq$ 7 days from study registration and $\leq$ 35 days from surgery.

6.1.4 Cohort assignment: Registered patients will be assigned sequentially to standard therapy (RT/temozolomide, **cohort 1**) or standard therapy + belinostat (RT/temozolomide/belinostat, **cohorts 2a and 2b**), depending on where we are in enrollment. The 1st 14 enrolled patients (irrespective of site of enrollment) will be assigned to **cohort 1** (standard therapy arm). Emory and JHU will offer entry to **cohort 2a** to patients but can alternatively also offer **cohort 1** entry for patients that refuse entry to the belinostat dose finding arm. A total of up to 30 patients can be enrolled to **cohort 1**. Up to 12 patients may be enrolled on **cohort 2a**. Entry onto **cohort 2b** (belinostat MTD arm) will start after **cohort 2a** have completed accrual and been followed for a minimum of 30 days following completion of concurrent RT/TMZ. In the special case where the first two patients within a dose level that cannot change further is enrolled and do not experience a DLT within 30 days of completing concurrent RT/TMZ, then when the 3rd patient is enrolled into cohort 2a, the next patient can then be enrolled before the 30 day post-RT/TMZ DLT assessment into either cohort 2a or 2b depending on whether the 3rd patient experiences a DLT in that time frame. 39-42 patients will be assigned to **cohort 2b** (belinostat MTD arm) so that a total of 45 patients will be treated at the expansion dose. Cohort assignment is given to the site as eligibility is confirmed. After cohort assignment, for patients assigned to **cohort 2a** or **2b**, the Emory or JHU investigational pharmacy will provide

belinostat to their respective infusion center prior to each treatment infusion for study subjects per each institution's SOP.

6.2 Investigator registration/requirements: Prior to recruitment of subjects to this trial, investigators must complete training as required per institutional IRB for participation on clinical trials along with protocol specific training. Each investigator must be registered (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) and maintain an "active" registration status.

6.3 Site registration/requirements

6.3.1 IRB: Investigators at each site will obtain IRB approval for this study and maintain this approval for the duration of the study treatment and follow up times. Documentation of initial and continued IRB approval will be submitted to the Winship Clinical Trials office.

6.3.2 Radiation Therapy: All institutions participating on this trial will need to be credentialed to use IMRT on the study. Previous credentialing for cooperative group and/or consortium trials (eg. RTOG, ABTC, etc.) is acceptable.

6.3.3 Neurocognitive certification: All study staff that will be administering neurocognitive testing will need to be certified as specified in section 7.2.1. Previous certification for administering these tests on other studies is acceptable after submission of documentation to the Winship Clinical Trials office.

7.0 STUDY EVALUATIONS

7.1 Summary of Active Monitoring Schedule

	Active Monitoring Schedule										
Tests and procedures	**Pre-reg**	**≤14 days prior to start of therapy**	**Cycle 0[10] (belinostat alone, 1 week, Cohort 2 only)**	**Cycle 1 (RT+TMZ±belinostat, 6 weeks, Cohorts 1 and 2)**						**Cycle 2-7 ≤7 days before each cycle (TMZ alone, 4 weeks each, Cohorts 1 & 2)[15]**	**After completion of adjuvant TMZ (Cohorts 1 and 2)**
				1	**2**	**3**	**4**	**5**	**6**		
Path diagnosis	X[2]										
H&P, weight, KPS		X			X[12]		X[12]		X[12]	X	X[17]
Height		X									
Neuro exam		X			X[12]		X[12]		X[12]	X	X[17]
Adverse event assessment		X		X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X	X[17]
Rad Onc consult	X[3]										
Neuro Onc consult	X[3]										
CBC w/diff		X[4]		X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X	
Chemistry[1]		X[4]		X[13]	X[13]	X[13]	X[13]	X[13]	X[13]	X	
Coags (PT/PTT)[5]				X[5]			X[5]				
MRI w/contrast	X[6]									X[16]	X[17]
MRSI		X[7]	X[7]			X[7]				X[7]	
Steroid/anti-Sz med documentation		X		X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X	
Serum pregnancy test		X[8]									

Medication diary			X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]		
Neurocognitive and QOL assessments		X[9]								X[9]	X[18]
IDS-SR		X[7]	X[7]			X[7]				X[7]	
Research sample submission		X[2]									

[1] Sodium, potassium, bicarbonate, chloride, BUN, creatinine, calcium, glucose, total bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase, albumin, total protein.

[2] Pathology diagnosis for study entry can be completed by institutional study pathologist. Representative H&E slide and unstained slides are to be submitted to Neuropathology at Emory University c/o Daniel Brat, MD within 30 days after registration.

[3] Either Rad Onc or Neuro Onc consultation needs to be completed at pre-registration. The other consultation can be completed ≤ 21 days before registration.

[4] To be completed ≤ 14 days prior to registration.

[5] For patients on Coumadin, PT will be performed on week 1 and week 4. Otherwise, PT and/or PTT will be performed only if clinically indicated.

[6] A diagnostic MRI scan with and without intravenous contrast will be done one week before the start of therapy if the immediate post-operative MRI scan was done > 28 days from registration. This is for RT treatment planning and establishment of a pre-treatment baseline.

[7] MRSI scan and IDS-SR to be completed ≤ 14 days prior to cycle 1 (**cohort 1**)/ ≤ 7 days prior to starting cycle 0 (**cohort 2**) (may be completed on day 1 of cycle 1 or cycle 0 depending on the cohort), after completion of cycle 0 (preferably on day 1 of cycle 1 but can be delayed to as late as day 3, if necessary) (**cohort 2 only**), during cycle 1 on day 15 ± 2 days and 4 weeks ± 7 days after completion of RT. No MRSI or IDS-SR beyond cycle 2. If scan is judged to be technically deficient, re-scanning may be performed within 2 days of the original attempt.

[8] To be completed only in women of childbearing potential. Test obtained ≤ 7 days prior to registration. May use a test result obtained for other clinically warranted indications if the test date is within the above time window.

[9] Neurocognitive and QOL are to be performed ≤ 7 days before starting cycle 0 & 4 weeks (± 2 weeks) after completion of cycle 1 (at pre-cycle 2).

[10] Cycle 0 needs to start within 7 days after registration.

[11] The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.

[12] To be performed every other week starting on week 2 of cycle 1.

[13] To be assessed weekly (by either Radiation Oncology or Neuro-Oncology) during cycle 1.

[14] Document steroids and anti-seizure meds weekly during cycle 1.

[15] May extend to up to cycle 13 of TMZ alone at physician discretion.

[16] Diagnostic MRI w/ and w/o contrast to be completed ≤ 7 days prior to starting cycles 2, 4, and 6 (cycles 8, 10, and 12 as well if necessary).

[17] Followups and diagnostic MRI w/ and w/o contrast to be completed 4 weeks after completion of adjuvant therapy (cycle 7 up to as late as cycle 13) when the last AE assessment will be made. Further followup schedule is suggested to be every 3 months x 6 (until approximately 2 years after RT) but can be modified at the discretion of the treating physician. Subsequent followups/MRIs will be determined by treating physician.

[18] To be performed every 6 months (± 1 month) from pre-cycle 2 assessment until progression (will attempt be obtain final assessment only if date of progression is > 3 months from previous assessment) or until approximately 2 years after pre-cycle 2 assessment (maximum of 4 additional assessments).

7.2 Neurocognitive Testing

7.2.1 Certification: All members of the study team that will be administering the

neurocognitive tests will need to be certified. Previous certification for any one of the following studies is sufficient: ACOSOG Z0300; ECOG E3F05; NCCTG N0574, N0577, or N107C; RTOG BR-0018, 0212, 0424, 0525, 0534, 0614, 0834, 0825 or the two phase III randomized motexafin gadolinium studies. However, while previous certification is acceptable, it is preferred that any study personnel that will be administering these tests undergo specific certification for this study. This certification process will be under the direction of Dr. Drenna Waldrop-Valverde (404-712-9487). Information on getting certification can be obtained from the Emory Clinical Trials office (404-778-1842).

7.2.2 Timing of Assessments: Evaluations will be performed ≤ 7 days before starting cycle 0 (cohort 2) or cycle 1 (cohort 1) (may complete on day 1 of cycle 0/1 depending on cohort), 4 weeks after completion of cycle 1, and every 6 months thereafter for approximately 2 years after RT completion. (See Table in section 7.1) In case of disease progression within 2 years from cycle 1, patients will be re-tested for the final time only if previous assessment was > 3 months from date of progression.

7.2.3 Tests to be administered: Hopkins Verbal Learning Test – Revised (HVLT-R), Controlled Oral Word Association test from the Multilingual Aphasia Examination (COWA), Trail Making Test A and B, and Recall and Recognition of Word List encoded from the HVLT-R. (see Appendix 4 for sample of each test)

7.3 Quality-of-Life (QOL) Testing: These questionnaires have been validated in the brain tumor population and used in other large, prospective studies for this patient population, providing a good potential comparison group for patients on this study. Subjects can opt out of this assessment if they so choose.

7.3.1 Timing of Assessments: Assessments will be performed ≤ 7 days before starting cycle 0 (cohort 2) or cycle 1 (cohort 1) (may complete on day 1 of cycle 0/1 depending on cohort), 4 weeks after completion of cycle 1, and every 6 months thereafter for approximately 2 years after RT completion. (See Table in section 7.1) In case of disease progression within 2 years from cycle 1, patients will be re-tested for the final time only if previous assessment was > 3 months from date of progression.

7.3.2 QOL Questionnaires: EORTC Quality of Life Questionnaire-Core 30/Brain Cancer Module-20 (EORTCQLQ30/BN20); M. D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT) (see Appendix 5 for sample of each questionnaire)

7.4 Self-assessment for depression

7.4.1 Timing of Assessments: Assessments will be performed with each MRSI scan starting ≤ 14 days before starting cycle 1 (**cohort 1**)/≤ 7 days before starting cycle 0 (**cohort 2**) (may complete on day 1 of cycle 0/1 depending on cohort), on day 1 of cycle 1 (preferably on day 1 of cycle 1 but can be delayed to as late as day 3, if necessary) (**cohort 2 only**), after 2 weeks of therapy in cycle 1, and 4 weeks after completion of cycle 1. (See Table in section 7.1). No assessment beyond cycle 2.

7.4.2 Questionnaire for assessment of mood: Inventory of Depressive Symptomatology (Self-Report) (IDS-SR) (see Appendix 6 for sample of questionnaire)

8.0 TREATMENT PLAN

8.1 Radiation Therapy

8.1.1 Timing of Radiotherapy: RT must begin ≤ 14 days from registration. Belinostat (varying doses x 5 days/cycle, q3week±1day x 3 cycles) will be initiated 7 days prior first RT dose for patients in cohort 2a and 2b. Daily oral temozolomide will start together with the first day of radiation. RT may start on M-Th for cohort 1 but must start on Monday or Tuesday for cohort 2a and 2b. Temozolomide is given every day during course RT (M-Su). Belinostat will be given on M-F or Tu-Sat depending on when 1st day of radiation is scheduled to be given for patient in cohort 2a and 2b (Mon. or Tues.). If an unanticipated single day break is necessary on a weekday during the course of RT when belinostat is scheduled to be given, belinostat will still be given on that day.

8.1.2 Certification: Standard and conformal techniques will be allowed in this study along with IMRT. To utilize IMRT on this study, an institution needs to be properly credentialed. Previous certification by the Radiological Physics Center (RPC) for use of IMRT on another protocol is acceptable.

8.1.3 Radiation Energy: Minimum photon energy is 6 MV with multiple ports designed and verified by simulation. Minimum SSD or SAD is 80 cm. If IMRT is utilized, 6 MV is preferred.

8.1.4 Target Volume Definitions

8.1.4.1 ICRU Definitions: ICRU terminology defines the gross tumor volume (GTV) and clinical tumor volume (CTV) as the extent of gross and microscopic disease, respectively. The planning target volume (PTV) is geometrically, not anatomically, defined and is an expansion of the CTV intended to account for uncertainty in patient positioning.

8.1.4.2 GTV1: This volume encompasses the edema and T2 hyper-intensity surrounding the main tumor mass as estimated from the T2-weighted or FLAIR postoperative MRI scan. By definition, this volume will always include all of GTV2.

8.1.4.3 GTV2: This volume encompasses the post-operative resection cavity (as seen on both T1 post-contrast and T2 sequences) plus any contrast enhancing volume or mass. Fusion of the pre-operative T1-weighted, contrast enhanced MRI is also encouraged to ensure inclusion of the pre-operative localized contrast-enhancement or mass within the GTV2. GTV2 may be modified to account for anatomic changes post-operatively to respect the anatomic structures within which the tumor was initially bound. For example, if a large tumor with mass effect has been resected, anatomically distant brain parenchyma may post-operatively be within the fusion-generated GTV2. GTV2 may be modified to exclude geographically distant brain parenchyma in this situation.

8.1.4.4 CTV1: This volume includes GTV1 plus a 0.5-1 cm margin (at discretion of

treating radiation oncologist). CTV1 may be anatomically confined, for example, to within the calvarium. However, high grade gliomas can invade most intracranial structures and should not be confined by the tentorium or an arbitrary midline. This expansion can be excluded from the brainstem and optic chiasm/nerves at the treating physician's discretion if there is not felt to be risk of extension into these regions.

8.1.4.5 CTV2: This volume includes GTV2 plus a 0.5 cm margin. By definition, this volume will always be completely encompassed by CTV1.

8.1.4.6 PTV1 and PTV2: These volumes are uniform 0.3 to 0.5 cm expansions of CTV1 and CTV2, respectively, to account for set-up uncertainty. PTV margin is institution dependent and differs based on patient set-up and image-guidance technique. It is not confined anatomically with the exception of cases which would otherwise exceed normal tissue tolerance (see below for normal tissue dose constraints). In 3D planning generally another 5-7 mm is added to block edge to account for penumbra to ensure full dose to the PTV.

8.1.5 Prescription Isodose: The prescription isodose surface (100% dose curve) shall encompass a minimum of 95% of the PTV. In addition, the entire PTV shall be encompassed by the 95% isodose surface. The dose uniformity guidelines below must be met for both the PTV1 and the PTV2 boost. If IMRT is used with an integrated boost, the PTV1 and the PTV2 boost will be treated concomitantly.

8.1.6 Tissue Heterogeneity: Calculations to take into account the effect of tissue heterogeneities are required.

8.1.7 Target Dose

8.1.7.1 Prescription dose: PTV1 will receive 4600 cGy in 23 fractions of 200 cGy per day and PTV2 will receive an additional 1400 cGy in 7 fractions of 200 cGy per day for a final total dose of 6000 cGy in 30 fractions.

8.1.7.2 Alternative prescription dose for IMRT techniques: Patients receiving IMRT may alternatively be treated with a simultaneous in-field boost plan to avoid 2 separate radiotherapy plans. PTV1 will receive 5100 cGy in 30 fractions of 170 cGy per day while PTV2 will simultaneously receive 6000 cGy in 30 fractions of 200 cGy per day.

8.1.8 Dose Uniformity: The entire PTV shall be encompassed within the 95% isodose surface as evaluated by dose volume histogram. Please note it is preferable that 95% or more of the PTV receives the prescribed dose. The uniformity guidelines shall be met for both the PTV 1 and the PTV2. In addition, none of the PTV2 should receive more than 110% of the prescription dose (i.e. 6600 cGy).

8.1.9 Time Considerations: Patients will receive one treatment per day, five days per week. All fields will be treated each day. At least two fractions must be given during the first week of treatment.

8.1.10 Simulation: A conventional CT or MRI simulator will be used for patient simulation. The patient shall be treated in the supine position with a head-holding device that is transparent to x-rays (thermoplast masks, bite-block, etc.) to ensure adequate immobilization and reproducible daily setup of the treatment position.

8.1.11 Organs at Risk (OARs): When possible, without shielding GTV/CTV/PTV, the listed OARs should receive more than the following doses: brainstem $\leq$ 6000 cGy (95% of volume $\leq$ 5400 cGy), optic nerves and optic chiasm $\leq$ 5500 cGy (99% of volume $\leq$ 5400 cGy), retina $\leq$ 4000 cGy, cervical spinal cord $\leq$ 5000 cGy, and lens $\leq$ 500 cGy. If possible, no more than 1% or 1 cc of the contralateral uninvolved brain should receive more than 3000 cGy. Also, no more than 1% or 1 cc of unspecified tissue outside of the PTV should receive > 110% of the prescribed dose. Planning organ at risk volumes (PRVs) are recommended such that the spinal cord should have 3-dimensional expansion by 5 mm while the optic nerves, optic chiasm, and brainstem should have a 3-dimensional expansion by at least 1 mm. The dose constraints to the PRVs will be the same as for their respective OARs as outlined above. Lower priority (lower priority than PTV coverage) include: parotids (entire volume) ≤ 10 Gy; oral cavity/lips/nasal cavity mean dose $\leq$ 20 Gy and < 1% receiving > 40 Gy; inner/middle ear mean dose $\leq$ 30 Gy and < 1% receiving > 50 Gy; and lens as low as reasonably possible. For example (for the lower priority OARs), typically 100% of the parotids should receive $\leq$ 10 Gy, but tumor coverage is of higher priority leading to cases where this dose may exceed 10 Gy.

8.1.12 Dose Calculation and Reporting: Patient treatment plans will need to be submitted electronically or by CD to Emory University, Dept. of Radiation Oncology, c/o Edi Schreibmann (404-778-5667). This will include submission of dose distributions and all target volumes and organs-at-risk. Exact instructions for submission of data can be made by contacting one of the investigators listed above. Submission of data should be completed within 30 days of RT completion.

8.1.13 IMRT Plan Verification: If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distribution can be re-computed for a phantom geometry.

8.1.14 Verification of treatment set-up: If 3D-CRT is used, port films of each field will be obtained and compared with initial simulation films at least weekly. Alternatively, after initial ports are taken of all fields (excluding vertex), an orthogonal pair of reference ports may be taken on a weekly basis. For IMRT, orthogonal pair of reference films is sufficient for the initial and subsequent ports. While setup checks using orthogonal pairs are required at least weekly, use of daily kV OBI equipment to check and reset the isocenter is encouraged.

8.2 Treatment schedule

Cycle 0 (day -7 to -3 relative to cycle 1, for cohort 2a and 2b only)

Agent	Dose level	Route	Schedule
Belinostat	varies	IV	1x/day for 5 days, may start Mon. or Tues.

Cycle 1 (~42 days + 4-6 week break)

Agent	Dose level	Route	Schedule
RT	60 Gy	Ext. beam	1x/day on M-F for 30 txs, may start M-Th for cohort 1 and M-Tu for cohort 2a/2b
Belinostat (for cohort 2a/2b only)	varies	IV	1x/day for 5 days, day 15-19 and 36-40 (± 1 day unless time is extended due to development of toxicity) on M-F or Tu-Sat during RT [1]
TMZ	75 mg/m^2	Oral	1x/day, 7 days/week on M-Su during RT [2]
4-6 week treatment break after completion of RT [3]			

Cycles 2-7 (28 days)[5]

Agent	Dose level	Route	Schedule
TMZ	150 mg/m^2	Oral	Days 1-5 for 28 day cycle (cycle 2)
TMZ	200 mg/m^2 [4]	Oral	Days 1-5 for 28 day cycle (cycles 3-7)

[1] 2nd and 3rd treatment course of belinostat (cohort 2a/2b only) will be given in week 3 and week 6 of RT/TMZ (during cycle 1). If the patient started on a Tuesday for their cycle 0 dosing, the 2nd and 3rd belinostat treatment course is permitted to start on a Monday (day 14 and day 35, respectively).

[2] Temozolomide (TMZ) will start with 1st RT treatment. TMZ will be given at standard dose 75 mg/m^2 with dose rounding as per institutional practice. If RT is extended due to holidays or unplanned breaks, up to 7 additional doses of TMZ can be given (up to 49 days). While a typical TMZ course will involve 42 days, the last dose will be on the last day of RT. This may result in as few as 40 days of TMZ if the first day of RT falls on a Monday and there are no breaks resulting in completion of RT on Friday of the 6th week of therapy.

[3] Rest period may extend up to 10 weeks, if necessary, to allow full recovery from potential toxicities. If toxicities have not recovered by 10 weeks, subject will be taken off study.

[4] If TMZ at 150 mg/m^2 is well tolerated on cycle 2 (adjuvant cycle 1), then subsequent cycles will utilize 200 mg/m^2.

[5] TMZ may be extended up to an additional 6 cycles (cycles 8-13) at the discretion of the treating physician if there are no other contraindications for continuation of TMZ and no evidence of progression.

8.2.1 Belinostat dose finding arm (cohort 2a): When a subject is enrolled on cohort 2a, they will be entered into the dose level that is currently open. Dosing will be based on actual body measurements. The dose levels are as follows:

Dose level 0: 750 mg/m^2 x 5 days q3week x 3 (during cycle 0 and 1)

Dose level 1: 1000 mg/m^2 x 5 days q3week x 3 (during cycle 0 and 1)

Dose level -1: 500 mg/m^2 x 5 days q3week x 3 (during cycle 0 and 1)

Starting dose will be at dose level 0. Assessment for DLT will be during cycle 0 and 1 and within 4 weeks of last belinostat drug dose. Rules for dose escalation/de-escalation are as follows for the 1st group of 3 subjects at each dose level:

1) 3 subjects will be initially enrolled at a dose level.

2) If 0 subjects experience a dose-limiting toxicity (DLT) ascribable to at least possibly be due to belinostat by the pre-cycle 2 laboratory evaluation and followup for the first 3 subjects at a dose level, then either the next higher dose level will be evaluated or enrollment will be complete for cohort 2a (if at dose level 1) with initiation of cohort 2b at dose level 1.

3) If 1 subject experiences a DLT ascribable to belinostat by the pre-cycle 2 laboratory evaluation and followup for the first 3 subjects at a dose level, then an additional 3 subjects will be enrolled at that same dose level. As stated in **section 6.1.4**, if the first two patients at a terminal dose level do not experience a DLT within 30 days of completing RT/TMZ, there will not be a delay until after the 3rd patient is fully evaluated before enrolling the next patient at the same dose, since the dosing scheme would not be any different. That patient will ultimately be assigned to cohort 2a if the 3rd subject experiences a DLT with further enrollment proceeding for two more patients at the same dose level in that same cohort or to cohort 2b if the 3rd subject does not experience a DLT with further expansion in that same cohort going forward.

4) If > 1 subjects experience a DLT ascribable to belinostat by the pre-cycle 2 laboratory evaluation and followup for the first 3 subjects at a dose level, then either the next lower dose level will be evaluated (if it had not previously been evaluated or only 3 subjects have previously been enrolled) or maximal tolerated dose (MTD) will be declared to be below dose level -1 (if at dose level -1) with suspension of cohort 2 (will not proceed to cohort 2b) or MTD will be declared to be at the next lower dose level (if 6 subjects have already been enrolled at that lower dose level) with initiation of cohort 2b at that next lower dose level.

If a 2nd group of 3 subjects is required for a dose level, then the following rules will apply:

1) If 0-1 of 6 subjects experiences a DLT ascribable to belinostat by the pre-cycle 2 laboratory evaluation and followup, then the next higher dose level will be evaluated if 6 subjects had not previously been evaluated at that dose level or the MTD will be declared with initiation of cohort 2b at this dose level.

2) If ≥ 2 of 6 subjects experiences a DLT ascribable to belinostat by the pre-cycle 2 laboratory evaluation and followup, then the next lower dose level will be evaluated if 6 subjects had not previously been evaluated at that dose level or the MTD will be declared to be below dose level -1 (if at dose level -1) with suspension of cohort 2 (will not proceed to cohort 2b).

Definition of DLT

a. Grade 4 thrombocytopenia, grade 4 anemia or grade 4 neutropenia lasting >7 days.

b. Any non-hematologic grade 3 or greater adverse event, excluding alopecia and venous thromboembolism.

Patients who develop deep vein thrombosis (DVT) or pulmonary embolism (PE) may receive anticoagulation and resume therapy with belinostat and temozolomide once clinically stable. Because DVT and PE are common complications among GBM and gliosarcoma patients, the first DVT and PE will not be considered DLTs. Recurrent DVT or PE on therapy will be considered a DLT.

c. Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte abnormalities such as hypocalcemia and hypophosphatemia (electrolyte abnormalities in this category need to be considered clinically significant to qualify as a DLT) that cannot be controlled by medical therapy will be considered dose limiting.

d. Grade 4 radiation-induced skin changes.

e. Failure to recover from toxicities to be eligible for re-treatment with belinostat and temozolomide ≤ 14 days of the last dose of the two drugs.

8.2.2 Bellinostat expansion arm (cohort 2b): Subject will receive the dose level determined based on results from cohort 2a.

8.2.3 Administration of belinostat: Belinostat will be given IV > 2 hours before RT on days when RT and drug are both given. The belinostat dosing in each 5 day course should be administered 24 hours apart (± 3 hours). Administration of drug will be per instructions in belinostat package insert. Briefly, drug will be reconstituted and then given in 250 ml normal saline over 30-45 minutes.

8.2.4 Administration of temozolomide: Temozolomide dosing will be based on actual body weight. Up to a 10% variation in the final prescribed temozolomide dose is allowable to help minimize the number of capsules needed for each dose per institutional standard. Temozolomide capsules should be taken preferably in the morning (on cycle 1) with up to 200 mL of water on an empty stomach one hour before or two hours after food. Evening/night dosing of TMZ right before bedtime can be used during adjuvant TMZ therapy (cycles 2-7 up to potentially cycle 13). If possible, temozolomide should be taken 1 hours before RT but the timing of the dose and dose levels are left to the discretion of the treating physician. Since temozolomide may cause nausea, an appropriate anti-emetic (e.g., 1 mg dose of granisetron or 4-8 mg of ondansetron) should be given once a day before the temozolomide. On days when patients do not have radiation, they should continue to take temozolomide in the morning on an empty stomach at approximately the same time as radiation days.

8.2.5 Pneumocystis jirovecii pneumonia [PJP (PCP)] prophylaxis: Since low dose temozolomide is immunosuppressive and associated with an increased risk of PJP, all subjects must receive prophylaxis during RT with concomitant temozolomide ± belinostat. Prophylaxis must be continued for at least two weeks after the completion of RT. The choice of prophylactic medications will be left to the discretion

of the treating physician. Options include atovaquone and dapsone. Based on NABTC experience, trimethoprim/sulfamethoxazole (Bactrim) appears to contribute to myelosuppression in patients on chemotherapy. Thus, this agent is not preferred. It may be used in patients who cannot tolerate other options listed above, although the final decision will be left to the discretion of the treating physician. The decision to continue PJP prophylaxis beyond the timepoints noted is left to the discretion of the treating physician. Subjects who continue to demonstrate lymphopenia after the continuous daily dosing of TMZ has been discontinued should be considered for ongoing prophylaxis.

8.2.6 Treating physician: Subjects will be treated as outpatients at protocol study sites. All treatments are prescribed/given by study physicians. During RT, subjects will be evaluated on a weekly basis. During the adjuvant TMZ phase, subjects will be evaluated on a q28 day basis.

9.0 DOSAGE MODIFICATION BASED ON ADVERSE EVENTS

Follow modifications based information given below until individual treatment tolerance can be ascertained. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. If an adverse event is not covered below, doses may be reduced or held at the discretion of the treating physician for the subject's safety. Dose adjustments for hematological adverse event are based on the blood counts obtained in preparation for the day of treatment.

9.1 Radiation therapy: While interruption due to acute radiation adverse events is unlikely given the type of radiation planned, individual reasons, such as major worsening of neurological or mental status or any other medical condition may preclude the continuation of radiotherapy. Resuming RT in this setting will be at the discretion of the treating physician. For example, cranial irradiation can be withheld for CNS adverse events or toxicity ≥ grade 3 attributable to radiotherapy. The overall time of interruption and overall time of radiotherapy must be recorded. If radiotherapy is interrupted, actions regarding dosing on concomitant temozolomide are described below:

- If administration of belinostat and/or temozolomide is interrupted, RT will proceed normally and no catch up days of belinostat and/or temozolomide will be given after end of RT.
- If RT extends beyond 42 days because of delays, temozolomide may be extended to a maximum of 49 days (at discretion of treating physician). If RT is still not completed, additional temozolomide beyond 49 days is not permitted.
- If RT is stopped for an adverse event felt clearly related to radiation and not belinostat/temozolomide, concomitant belinostat/temozolomide should be continued as per protocol unless PD occurs.

9.2 Concomitant treatment: If the attribution of the adverse event can be clearly linked to only one of the two drugs, dose modifications for that drug only should be followed.

9.2.1 Dose modification criteria for temozolomide during RT (cycle 1): Concurrent temozolomide dose for cycle 1 is 75 mg/m2 given every day (including weekends)

over the RT course (up to a maximum of 49 days). Maximum dose reduction is 50% of the starting dose. If significant toxicity is still experienced at 50% of the starting dose, temozolomide will be discontinued.

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified		
Dose modification criteria for temozolomide (cycle 1)		
CTCAE Category	**Adverse Event**	**Dosage Change**
Blood/bone marrow	Grade 2 - ANC<1500-1000 or PLTS<100,000-50,000	Continue RT but omit TMZ until ANC≥1500 and PLTS≥100,000, ↓TMZ dose by 15%.
	Grade 3 - ANC<1000-500 or PLTS<50,000-25,000	Continue RT but omit TMZ until ANC≥1500 and PLTS≥100,000, ↓TMZ dose by 25%.
	Grade 4 - ANC<500 or PLTS<25,000	Hold RT and TMZ. Resume RT when ANC ≥500 & PLTS≥25,000 and TMZ when ANC≥ 1500 & PLTS≥100,000, ↓TMZ dose by 50%.
Gastrointestinal	Grade 2 - Nausea/vomiting on optimal anti-emetics	TMZ may be held until recovery to grade 0-1 at physician's discretion.
	Grade 3 - Nausea/vomiting on optimal anti-emetics	Omit TMZ until grade 0-2 (or ≤1 grade of baseline), ↓TMZ dose by 25%.
	Grade 4 - Nausea/vomiting on optimal anti-emetics	Omit TMZ until grade 0-2 (or ≤1 grade of baseline), ↓TMZ dose by 50%.
Non-hematologic Other	Grade 2	TMZ may be held until recovery to grade 0-1, ↓TMZ dose by 15% at physician's discretion.
	Grade 3	Omit TMZ until grade 0-2 (or ≤1 grade of starting value for pre-existing abnormalities), ↓TMZ dose by 25%.
	Grade 4	Omit TMZ until grade 0-2 (or ≤1 grade of starting value for pre-existing abnormalities), ↓TMZ dose by 50%.
Development of alopecia does not require dose modification		

9.2.2 Dose modification criteria for belinostat before and during RT (cycles 0 and 1): For cycle 0, belinostat will be given at the current dose level (based on where we are in the study) for 5 consecutive days. For cycle 1, belinostat will be given at the current tolerated dose for 5 consecutive days at least 3 weeks (± 1 day) from the start of the previous 5 day treatment (time may be extended based on criteria below). Only 2 dose reductions are allowed. If criteria for dose reductions are met for patients already at dose level -1, belinostat should be discontinued.

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified		
Dose modification criteria for belinostat (cycles 0 and 1)		
CTCAE Category	**Adverse Event**	**Dosage Change**
Blood/bone marrow	Grade 2/3 - ANC<1500-500 or PLTS<100,000-25,000	Continue RT but omit belinostat until ≤ grade 1 (ANC≥1500 & PLTS≥100,000), ↓belinostat by 1 dose level. D/C belinostat if recovery to ≤ grade 1 takes >14 days.

	Grade 4 - ANC<500 or PLTS<25,000	Hold RT and belinostat. Resume RT when ANC≥500 & PLTS≥25,000 and belinostat when ANC≥1500 & PLTS≥100,000, ↓belinostat by 2 dose levels. D/C belinostat if recovery to ≤ grade 1 takes >14 days.
Gastrointestinal	Grade 3/4 - Nausea/vomiting on optimal anti-emetics	Omit belinostat until ≤grade 1 (or ≤1 grade of baseline), ↓belinostat by 1 dose level. D/C belinostat if recovery to ≤ grade 1 takes >14 days.
Non-hematologic Other	Grade 3/4	Omit belinostat until ≤grade 1 (or ≤1 grade of baseline), ↓belinostat by 1 dose level. D/C belinostat if recovery to ≤ grade 1 takes >14 days.
Development of alopecia does not require dose modification		

9.2.3 Belinostat dose reduction levels before and during RT (cycles 0 and 1): If criteria for dose reductions are met for patients already at dose level -1, belinostat should be discontinued.

Dose Level	Belinostat
-1	500 mg/m^2/day – 5 consecutive days q3weeks x 3 (cycle 0 and 1)
0	750 mg/m^2/day – 5 consecutive days q3weeks x 3 (cycle 0 and 1)
1	1000 mg/m^2/day – 5 consecutive days q3weeks x 3 (cycle 0 and 1)

9.3 Adjuvant treatment: If the attribution of the adverse event can be clearly linked to only one of the two drugs, dose modifications for that drug only should be followed.

During adjuvant therapy only, patients who require resection for radiation necrosis without evidence of recurrent tumor may continue to receive protocol therapy as long as they are not off study drug for >6 consecutive weeks.

9.3.1 Dose modification criteria for temozolomide after RT (cycles 2-7 up to cycle 13): Adjuvant temozolomide dose for cycle 2 is 150 mg/m^2 given days 1-5 of 28 day cycle. This dose is used even if temozolomide dose reductions or treatment delays were necessary during cycle 1 as long as other criteria at time of starting cycle 2 do not preclude beginning adjuvant temozolomide therapy. If tolerated, subsequent cycles will increase dose to 200 mg/m^2 given days 1-5 of 28 day cycles. Maximum dose reduction is 50% of the starting dose (75 mg/m^2 if dose reduction required after cycle 2 or 100 mg/m^2 if dose reduction required after cycle 3 or later). If significant toxicity is still experienced at 50% of the starting dose, temozolomide will be discontinued.

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified

Dose modification criteria for temozolomide at time of retreatment		
CTCAE Category	**Adverse Event**	**Dosage Change**
Blood/bone marrow	ANC<1500 or PLTS<100,000	Hold TMZ until ANC≥1500 and PLTS≥100,000, ↓TMZ dose based on nadirs (see table below based on interim AEs). If no recovery for > 4 weeks then discontinue TMZ.
Non-hematologic Other	Grade 3/4	Hold TMZ until recovery to grade 0-1, ↓TMZ based on interim AEs (see table below). If no recovery for > 4 weeks then discontinue TMZ.

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified		
Dose modification criteria for temozolomide based on interim adverse events		
CTCAE Category	**Adverse Event**	**Dosage Change**
Blood/bone marrow	Grade 3 - ANC<1000-500 or PLTS<50,000-25,000	↓TMZ dose by 25%. (Hold TMZ based on above table's criteria)
	Grade 4 - ANC<500 or PLTS<25,000	↓TMZ dose by 50%. (Hold TMZ based on above table's criteria)
Gastrointestinal	Grade 3 - Nausea/vomiting on optimal anti-emetics	↓TMZ dose by 25%.
	Grade 4 - Nausea/vomiting on optimal anti-emetics	↓TMZ dose by 50%.
Non-hematologic Other	Grade 3	↓TMZ dose by 25%. (Hold TMZ based on above table's criteria)
	Grade 4	↓TMZ dose by 50%. (Hold TMZ based on above table's criteria)

10.0 ANCILLARY TREATMENT/SUPPORTIVE CARE

10.1 Antiemetics: Since TMZ may cause nausea, it is suggested that an appropriate antiemetic (e.g., 1 mg dose of granisetron, or 4 mg of ondansetron, or other) be given one hour before TMZ. As an alternative, antiemetic may be used on the first 3 days of concomitant RT/TMZ and the first 3 days of adjuvant TMZ, with any further need determined by the treating physician based on perception of clinical need. Additional symptoms will be managed as per standard antiemetic guidelines.

10.2 Antidiarrheals: Use of loperamide (Imodium) for treatment-induced diarrhea is strongly encouraged. Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear

fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops, discontinue further treatment with belinostat.

10.3 Supportive care: 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 (i.e., antidiarrheals, analgesics, antiemetics) received from the first day of treatment until 30 days after the final dose will be recorded on the concomitant medication form. Adequate hydration should be maintained in the setting of dysgeusia (popsicles and Gatorade have been found to be useful by some investigators).

10.4 Colony stimulating factors: These factors should not be used prophylactically to prevent granulocytopenia. Growth factors are not permitted to induce elevations in neutrophil count for the purposes of (1) administration of temozolomide on the scheduled dosing interval, or (2) allowing treatment with temozolomide at a higher dose, or (3) avoiding interruption of the treatment during concomitant radiotherapy. The therapeutic use of colony stimulating factors will be based on clinical judgment and may be appropriate in patients with a documented infection in the presence of severe granulocytopenia (granulocyte count less than 500/mm^3). Use of colony stimulating factors in clinically indicated situations should be consistent with product labeling and recorded on the concomitant medication form. 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): 1-19 AND American Society of Clinical Oncology/American Society of Hematology 2007 Clinical Practice Guideline Update on the Use of Epoetin and Darbepoetin J Clin Oncol 25(34): 1-17. (See www.asco.org web site)

10.5 Erythropoietin: RBC support with erythropoietin can be used at the physician's discretion.

10.6 Pneumocystis jirovecii pneumonia (PJP [PCP]) prophylaxis: Pneumocystis jirovecii pneumonia has developed in patients when taking concomitant temozolomide and steroids. This is of concern especially for lymphopenic patients. Prophylactic treatment is required for the concomitant RT/temozolomide ± belinostat phase of the study (cycle 1). See section 8.2.3 for details.

10.7 Surgery: If neurosurgical management is required for reasons not due to tumor progression, these procedures must be documented, including the indications for surgery, the surgical operative note and pathology report.

10.8 Corticosteroid treatment: Dosages and evaluation date of dexamethasone use must be recorded on concomitant steroid, anticonvulsant, and antiemetic medication form. Corticosteroids should be used in as low a dose as possible. At progression of disease, corticosteroid choice and dosages are at the discretion of the patient's physician.

10.9 Treatment of fatigue: Patients experiencing profound fatigue may use medications such as modafinil at the discretion of the treating physician.

11.0 TREATMENT EVALUATION

11.1 Objectives – (see section 2.1-3)

11.2 Imaging assessment

11.2.1 Conventional MRI scans: Diagnostic MRI scans w/ and w/o contrast will be utilized to assess for response. It is preferred that scans be performed on a 3 T scanner, if possible (minimum scanner field strength is 1.5 T). Standard sequences will be obtained including T1 pre- and post-gadolinium (including at least one post-contrast set that is a high resolution, volumetric acquisition), T2, T2 GRE, FLAIR, DWI including ADC map, and DSC perfusion imaging. These studies will be obtained at the schedule outlined in section 7.1.

11.2.2 MRSI: To obtain the highest resolution and sensitivity possible, we will adapt and optimize 3D-EPSI/GRAPPA sequence from U of Miami. Whole brain EPSI will be performed as described previously [75] on a Siemens 3T TRIO/TIM systems using 32-channel head coils. The basic EPSI sequence consists of a slab selective spin-echo with Ernst angle excitation pulse (~73˚), and an oscillating read gradient with phase-encoding in 2 dimensions. A 3 pulse 'WET' [76] water suppression scheme is used, and lipid suppression is accomplished using a slab selective short T_I (198 ms) inversion recovery (STIR) scheme. The STIR pulse also reduces underlying macromolecule signals in the spectrum and actually decreases the sensitivity of the metabolite signals to potential changes in T_1 relaxation times [77, 78]. The pulse sequence also includes an interleaved small flip angle (20˚) water reference excitation. The changes include: (a) a shorter echo time will be used (17 vs. 70 ms) to allow optimal detection of MI and other compounds, and (b) GRAPPA spatial encoding (implemented as in ref [79]) with an acceleration factor of ~2 will be used, resulting in scan times of ~12 min for whole brain 3D images. Scan parameters are as follows: TR/TE/TI = 1550/17/198 ms, matrix size 50x50 (in-plane) x 18 partitions (along z); 280x280 mm^2 FOV, 180 mm slice thickness; 140mm excitation slab thickness, resulting in a nominal voxel size of 0.44x0.44x0.56 ≈ 0.108 cm^3. Prior to data acquisition, field-map based high order shimming (up to 2nd order) will be performed. In addition to the EPSI, sequences that will be run include two FLASH/SPGR sequences with 4˚ and 23˚ flip angles which will be used for water content determination [80], and a T_1-weighted MPRAGE at an isotropic resolution of 1 mm (TR/TE/TI/FA = 2150/4.4/1100ms/8˚) will be used for tissue segmentation using FSL/FAST [81] and spatial registration. Intra- [12] and inter- [82] site reproducibility assessments of this sequence have been determined recently. Voxel-based coefficients of variation for the major metabolites are typically in the 5-10% range. Metabolite and water reference images will be reconstructed in a fully automated manner using the MIDAS (Metabolic Imaging Data Analysis System) package [83, 84]. This will include spatial smoothing and interpolation of the metabolite images to 64x64x32 points. Spectra in voxels for which the water signal intensity linewidth was 15 Hz or less will be analyzed using an automated parametric spectral analysis procedure [85] to determine volumetric metabolic images of NAA, MI, Cr, Cho, and Lac. Metabolite concentrations in arbitrary units will be calculated by ratio to the brain water signal from the same ROI, with adjustment for brain water content as determined from the FLASH sequences [80]. Quantitative metabolic images will be output from MIDAS for import into Velocity AI. MRSI studies will be obtained at the schedule outlined in section 7.1.

11.3 Response criteria

11.3.1 Measurable Disease: Bidimensionally measurable lesions with clearly defined margins by MRI scan.

11.3.2 Evaluable Disease: MRI assessment (compared to pretreatment scan) for evaluable disease (i.e., contrast enhancing mass on MRI) which is not bidimensionally measurable but clearly evaluable for response to therapy.

11.3.3 Objective Status, To Be Recorded at Each Evaluation: If there are too many measurable lesions to measure at each evaluation, choose the largest two to be followed before a patient is entered on study. The remaining lesions will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

11.3.4 Response Definitions

11.3.4.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. No evidence of non-evaluable disease. All measurable, evaluable and non-evaluable lesions and sites must be assessed using the same techniques as baseline. Patients must be on no steroids.

11.3.4.2 Partial Response (PR): (Measurable disease only) Greater than or equal to 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed using the same techniques as baseline. *The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.*

11.3.4.3 Stable Disease (SD): Does not qualify for CR, PR, or progression. The designation of SD requires a minimum of 8 weeks duration (2 assessment of stable disease 8 weeks apart). All measurable and evaluable sites must be assessed using the same techniques as baseline. The steroid dose at the time of the scan evaluation should be no greater than the maximum dose used in the first 8 weeks from initiation of therapy.

11.3.4.4 Progressive Disease (PD): 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR clear clinical worsening or failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer). While PD is defined by measuring the product of 2 dimensions as a surrogate for volume, the actual volume of each lesion will also be determined and results correlated with the bidimensional product. <u>NOTE: Increasing contrast enhancing disease in months 1-3 (potentially up to month 6) post-RT may represent pseudo-progression. Because of difficulties in the interpretation of pseudo-progression on MRI, the first post chemoradiation scan should NOT be used to declare progression. Progressive worsening on subsequent imaging</u>

studies usually distinguishes true progression from pseudo-progression. In particular, DCE perfusion imaging may be helpful at distinguishing true and pseudo-progression. If the rCBV map does not show evidence of increased perfusion in regions with increasing contrast-enhanced lesion(s), then pseudo-progression is favored and patient may be maintained on study. Subsequent increases up to 6 months post-RT will be evaluated on a case-by-case at a multi-disciplinary tumor board of the respective institution to assist in making a determination regarding true versus pseudo-progression.

11.3.4.5 Regressive Disease (REGR): (Evaluable disease only) Unequivocal reduction in extent of contrast as compared to baseline-enhancement or a decrease in mass effect as agreed upon independently by primary physician and quality control physicians; no new lesions.

11.3.4.6 Unknown: Progression has not been documented and one or more measurable or evaluable sites have not been assessed.

11.4 Best Response: This will be calculated from the sequence of objective statuses. For patients with all disease sites assessed every evaluation period, the best response will be defined as the best objective status as measured according to section 11.5. Determination of best response is not applicable for patients without evaluable disease.

11.5 Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam, as compared with the baseline assessment, that should coincide with objective measurement of tumor size.

NEURO EXAM STATUS (compared to pre-treatment exam)	
Better	Must be on stable or decreasing dose of steroids
Same	Failure to qualify for better or worse
Worse	Include patients requiring increasing steroid doses to remain stable

11.6 Performance Status: Patients will be graded according to Karnofsky Performance Status (see Appendix 3).

11.7 Time to Treatment Failure: From date of registration to the date of first observation of PD (as defined in section 11.5), non-reversible neurologic progression or permanently increased steroid requirement (applies to SD only), death due to any cause, or early discontinuation of treatment.

11.8 Survival Time: From date of registration to date of death due to any cause.

11.9 Progression Free Survival Time: From date of registration to date of progression or death.

12.0 ADVERSE EVENT REPORTING

12.1 Definitions

12.1.1 Adverse Event Definition - An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (eg, including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

12.1.2 Serious Adverse Event Definition - A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (eg, surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor

medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

12.2 Procedures for AE and SAE Reporting

The sponsor-investigator or authorized designee must report all serious adverse event (SAE) regardless of relationship with any study drug or expectedness to Spectrum Pharmaceutical as soon as possible, but no later than 5 calendar days of the observation or awareness of the event.

Sponsor-investigator must also provide Spectrum Pharmaceutical with a copy of all communications related to the Study or Drug with the applicable regulatory authority, including, but not limited to, telephone conversation logs, as soon as possible but no later than 5 calendar days of that communication.

Spectrum Pharmaceutical will confirm receipt of SAE reports or other communications within one (1) business day. If confirmation is not received, then sponsor-investigator will contact Spectrum to determine if the original report needs to be re-sent.

In addition the sponsor-investigator or authorized designee will forward a report to Spectrum Pharmaceuticals within 7 calendar days all reports of:

- PREGNANCY (IN PATIENT OR PARTNER) - acknowledging that this is not serious unless a serious outcome is seen (e.g. miscarriage, congenital anomaly).
- OVERDOSE - acknowledging that this is not serious unless a serious outcome occurs.

All SAEs should be recorded on a MedWatch 3500a Form and faxed to:

Hui-Kuo Shu, MD c/o Kasia Kopcewicz (Emory) and Nikki Brumbelow (John Hopkins)
Contact Information: Emory: TEL: 404-778-2981 Fax: 404-778-4389

John Hopkins: TEL: 404-778-5747 Fax: 404-778-0417

AND:

Others (as required by local site)

The sponsor-investigator or authorized designee will forward SAE reports from all sites to the Emory IRB per IRB reporting requirements and to Spectrum Pharmaceuticals within the time frame noted above.

MedWatch 3500a Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Spectrum Pharmaceuticals may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that belinostat caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to belinostat administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to belinostat administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

12.3 Attribution

The Principal Investigator or his designee will document his/her opinion and any supporting laboratory and clinical information of the potential attribution of the study drug to any grade 3 or greater toxicity based on the following guidelines:

12.3.1 Unrelated

This category applies to those toxicities that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.)

12.3.2 Unlikely (*must have any two criteria*)

In general, this category can be considered applicable to those toxicities that are judged to be unrelated to the test drug. A toxicity may be considered unlikely if or when:

1. It does not follow a reasonable temporal sequence from administration of the test drug;
2. It could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does not follow a known pattern of response to the test drug;
4. It does not reappear or worsen when the drug is re-administered.

12.3.3 Possible (*must have any two criteria*)

This category applies to those toxicities for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. A toxicity may be considered possibly related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It does follow a known pattern of response to the test drug.

12.3.4 Probable (*must have any two criteria*)

This category applies to those toxicities that are felt with a high degree of certainty to be related to the test drug. A toxicity may be considered probably related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose. There are important exceptions when a toxicity does not disappear upon discontinuation of the drug,

yet drug-relatedness clearly exists (e.g. bone marrow depression, fixed drug eruptions, tardive dyskinesia);
4. It follows a known pattern of response to the test drug.

12.3.5 Definite (*must have all four criteria*)

This category applies to those toxicities that are felt to be incontrovertibly related to the test drug. A toxicity may be considered definitely related if and when:

1. It follows a reasonable temporal sequence from administration of the test drug;
2. It could not reasonably be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject;
3. It disappears or decreases on cessation or reduction in dose with re-exposure to drug. (Note: this is not to be construed as requiring re-exposure of the subject, however, a category of definitely related can only be used when a recurrence is observed.)
4. It follows a known pattern of response to the test drug.

The Emory IRB will be notified of the event promptly per Emory IRB requirements.

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 4.0, as a guideline.

12.4 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the subject's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

12.5 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. The sponsor-investigator must be informed as soon as possible. Spectrum Pharmaceuticals must also be contacted by the sponsor-investigator as soon as possible after the sponsor-investigator has been informed. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

13.0 DATA AND SAFETY MONITORING PLAN (DSMP)

13.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Winship Cancer Institute Data Safety Monitoring Board:

The study will also be followed by the Winship Cancer Institute Data Safety Monitoring Board to allow for local review and confirmation of proper study execution and safety measures.

13.2.1 The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Since this is as study not run by th Phase I Working Group, the PI or designee must obtain approval from the DSMC for dose escalation. The PI will provide an update on

all relevant safety data of patients entered to a dose level to the DSMC when dose escalation is planned.

13.2.2 Procedures to assure data integrity and protocol adherence

13.2.2.1 Imaging and clinical data will be analyzed in a quarterly meeting of investigators, clinical research coordinators and regulatory personnel.

13.2.2.2 Adverse event reporting will utilize NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and is detailed in section 12.0 above.

13.2.2.3 Study Team Oversight: The study progress in terms of enrollment, activity of current patients under active treatment, observed toxicities will be reviewed in the monthly Emory Neuro-oncology Working Group. Here there will be random and selected case report form and chart review. Special and problematic items requiring additional attention will be addressed in separate sessions of the Neuro-oncology Working Group occurring up to weekly including selected study investigators, clinical research coordinators and regulatory personnel.

13.2.2.4 Training of investigators, clinical research coordinators and regulatory personnel at all sites will be performed by one of the principal investigators utilizing the written protocol and a summary of pertinent treatment activities. Completion of the training of investigators, clinical research coordinators and regulatory personnel will be documented on a study training log.

13.2.2.5 External Site Management: Enrollment will occur at Johns Hopkins University

- Monitoring of Study Activity: Monitoring of study activity will occur by monthly review of enrollment activity of current patients under active treatment, observed toxicities by the investigator, clinical research coordinator and regulatory personnel at Johns Hopkins. The results of this review will be summarized and shared and logged monthly in written form (and verbal form when needed) with the Emory investigators.

- Investigator Communication: Verbal investigator communication between Emory and Johns Hopkins will occur and be logged quarterly to discuss the content mentioned above.

- Reporting of Adverse Events Occurring at Johns Hopkins: The criteria and methods of collecting adverse event data outlined in section 12.0 will apply at Johns Hopkins also.

    - The Johns Hopkins Principal Investigator (PI) is responsible for review and assessment of all adverse events at their site as specified in the protocol. AEs, SAEs (initial and follow ups), and UPs will be reported to the

Emory Sponsor as per protocol requirements including reporting SAEs and UPs within 24 hours of the participating site becoming aware of the event.

- The Johns Hopkins site will submit applicable reporting forms (e.g. MedWatch Form 3500A, Emory Reportable Event Assessment Form, or protocol specific SAE reporting form) to the Winship regulatory staff. The Sponsor-Investigator (S-I) must review and sign off on the event and return to Winship regulatory staff. Regulatory will review the assessment to determine Institutional Review Board (IRB) and/or FDA reporting requirements.
- The Johns Hopkins site is also responsible for the following:
  - Report events, as applicable, to their IRB.
  - Submit all acknowledgements of reports submitted to their IRB to the Winship regulatory staff.
  - Resolve all queries related to the SAE report in a timely manner.
  - Maintain copies of each event reported in the subject's study records.
  - Enter events on an Adverse Event worksheet in the subject's study records.
  - Enter AEs into Oncore® in a timely manner.
  - Enter SAEs and UPs into Oncore® in the SAE category, in a timely manner.
- Winship regulatory staff is to follow the IRB policies and procedures, available on the Emory IRB website, and all FDA reporting requirements as applicable.

13.3 On-site Audits

Regulatory authorities, the IRB and Spectrum Pharmaceutical's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be

guaranteed by the investigator, who must provide support given reasonable notice at all times for these activities.

The following applies for monitoring of Sub-sites:
At the study initiation, the PI, regulatory specialist, and research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings will include the investigators, the clinical research coordinator and the regulatory affairs coordinator will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain one spread sheet which will summarize all the patient data for patients actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual patient. The spread sheet will be shared with Emory PI. Teleconferences will be conducted at least once monthly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. The minutes from the teleconference will be maintained in the regulatory binder for the study. In addition electronic copies will be sent via email to the principal investigators at each site. Chart reviews will be performed on selected cases from the participating site to confirm that the data collection is accurate.

Winship's Multi- Site Coordinator will perform remote quarterly monitoring of participating sites' data and will perform an on-site yearly monitoring visit as necessary per site enrollment. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies

14.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

14.1 Trial Design: The primary study objectives are as follows: 1) For **cohort 1**, we will use a support vector machine approach to determine an MRSI 5-metabolite profile at week 3 that is predictive of prolonged PFS, 2) For **cohort 2a**, we will determine the MTD for use of belinostat during cycle 0-1 and 3) For **cohort 2b**, we will determine if MRSI biomarkers at week 3 can predict improved PFS of GBM patients in belinostat responders versus non-repsonders. Initial MRSI scan is obtained pre-treatment. The week 3 MRSI scan is performed following the initial belinostat treatment window (**cohort 2** only) and after 2 weeks of chemoRT ± belinostat (**cohorts 1 and 2**). Based on our preliminary experience with vorinostat/TMZ in recurrent GBM patients, we anticipate approximately 40% of subjects treated with belinostat will exhibit restoration of MRSI metabolites toward values seen in the normal brain after 1 week (MRSI-responder). We have further preliminary data demonstrate that MRSI-responders is also detectable after 2 weeks of vorinostat/XRT/TMZ and would expect a similar finding with an alternative HDACi such as belinostat. Our endpoint is progression-free survival (PFS). Based on previous results, 40% of patients will be alive and free from progression at 9 months with standard therapy (XRT/TMZ). We assume that metabolic non-responders will have a PFS at 9 months of 40% (same as patients receiving standard therapy). With the proposed sample size of 45 belinostat subjects (estimated to include 18 responders and 27 non-responders) and alpha = 0.05 (at the significance level of 0.05), we will have 79% power to detect a 40%

or more increase in (>= 80%) PFS at 9 months in our belinostat subjects (MRSI-responders versus non-responders). Additional MRSI scans are done 7 days after initiation of belinostat alone (cycle 0) and 4 weeks after completion of XRT+TMZ. Secondary/exploratory study objectives will involve assessing our serial MRSIs and determining whether changes in the metabolite maps can predict survival and ancillary (mood/neurocognitive/QOL) outcomes.

14.2 Accrual rate: The anticipated rate of accrual will be 2-3 patients/month between Emory and Johns Hopkins. This will allow full accrual of 90 patients (cohort 1 + cohort 2) over a period of 3 years.

14.3 Criteria for removal from trial: All reasons for discontinuation of treatment must be documented.

14.3.1 Progression of disease as defined in section 11.3.

14.3.2 Unacceptable toxicity requiring treatment discontinuation as defined in section 9.

14.3.3 Patient may withdraw from study at any time for any reason.

14.3.4 Medical or psychiatric illness which in the investigator's judgment renders the patient incapable of further therapy.

14.4 Adverse event stopping rule: Rules for finding the MTD for belinostat given with RT/TMZ (**cohort 2a**) was previously outlined (**Section 8.2.1**). This rule outlined below will only be applied to patients enrolled in **cohort 2b**. If 4 out of the first 12 or 8 out of the first 24 patients or if at any time after the first 24 patients are enrolled, 33% or more patients experience a dose limiting toxicity (DLT) (as defined below), the study team will review the data to determine the proper course of action including potential closure of the study.

Definition of DLT

a. Grade 4 thrombocytopenia, grade 4 anemia or grade 4 neutropenia lasting >7 days.

b. Any non-hematologic grade 3 or greater adverse event, excluding alopecia and venous thromboembolism.

Patients who develop deep vein thrombosis (DVT) or pulmonary embolism (PE) may receive anticoagulation and resume therapy with belinostat and temozolomide once clinically stable. Because DVT and PE are common complications among GBM and gliosarcoma patients, the first DVT and PE will not be considered DLTs. Recurrent DVT or PE on therapy will be considered a DLT.

c. Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte abnormalities such as hypocalcemia and hypophosphatemia (electrolyte abnormalities in this category need to be considered clinically significant to qualify as a DLT) that cannot be controlled by medical therapy will be considered dose limiting.

d. Grade 4 radiation-induced skin changes.

e. Failure to recover from toxicities to be eligible for re-treatment with belinostat and temozolomide ≤ 14 days of the last dose of the two drugs.

14.5 Statistical analysis of MRSI scans: We will evaluate absolute metabolite levels as well as their fractional change on an MRSI study after early treatment with belinostat + chemoradiation. While our primary analysis will be to determine whether MRSI after 3 weeks of therapy (belinostat alone during cycle 0 and 2 weeks of chemoradiation) can signal whether a patient will respond well to this therapy, we will also examine whether an MRSI obtained after the initial belinostat alone treatment window is predictive of good outcomes to evaluate for changes produced by belinostat in isolation of effects from other therapies. While single metabolite changes will be assessed, composite metabolite changes are more likely to be predictive. An SRI score (0-5.0) will be generated that sums fractional changes in metabolite levels (fractional increases in NAA, MI, Cr and decreases in Cho, Lac up to a maximum of 1.0 per metabolite) from three different regions: (1) only the contrast-enhancing residual tumors; (2) 1 cm expansion around the contrast-enhanced tumors; and (3) all abnormal tumor area in pre-contrast T2-weighted images. Based on preliminary data in recurrent GBM patients, SRI scores > 0.80 may represent a good cutoff for a positive response to belinostat. The SRI score at the end of week 3 (primary analysis) and week 1 (secondary analysis) will be used to determine responders (SRI > 0.80) and non-responders (SRI ≤ 0.80). The logistic regression model will be applied to compare the primary end point, progression-free survival (PFS) at 9 months, between the responder and non-responder groups, adjusting for potential confounding factors. The rationale choosing PFS at 9 months rather than 6 months is to avoid pitfall of pseudoprogression that occurs in about 35% of GBM patients in the control group with TMZ+XRT. We also plan to conduct additional survival analyses by modeling the time to event (death) data with a Cox proportional hazards model to test whether the survival times differ significantly between the two groups (responder vs. non-responder), while controlling for other potential risk factors for survival. In addition to the dichotomized predictor (responder vs. non-responder) based on SRI score, we also hypothesize that a higher SRI score (as a continuous variable) will be predictive of longer OS and survival time. Therefore, we will also consider the continuous SRI score as the predictor in the logistic regression model and the Cox's proportional hazards model. More sophisticated modeling with support vector machine will also be done to attempt to develop better predictors based on the same 5 metabolites mentioned earlier to predict outcomes (PFS and OS) after belinostat therapy.

14.6 Statistical analysis of depression scale, neurocognitive function and QOL scores: Linear mixed effects models will be applied to model the repeatedly measured score from each assessment and/or test over time. We hypothesize that changes in individual and/or composite metabolite levels will be predictive of the temporal changing patterns in the scores on the depression self-report, neurocognitive functional tests and QOL assessments. Changes in individual and multiple metabolite levels within normal brain surrounding the region of the tumor will be evaluated with scores on these assessments using logistic regression models.

14.7 Statistical analysis of biological correlates: The following markers, if assessed as part of the standard clinical pathologic evaluation of GBMs: 1) EGFR amplification and PTEN status by FISH, 2) p53 status and isocitrate dehydrogenase 1 (IDH1) mutation status by immunohistochemistry (IHC), and 3) MGMT methylation status by methylation-specific PCR,,will be used to determine whether they can predict response to belinostat or overall outcomes (PFS or OS). In addition, baseline levels of histone acetylation at H3 (Lys18) and H4 (Lys8) will be determined by IHC and scored semi-quantitatively as follows: 1, weak/negative; 2, medium; 3, strong; and 4, very strong. An IHC score will be calculated by multiplying the percentage of positive tumor cells (0-100) by staining intensity (1-4) producing a total range

of 0–400. Two researchers will make independent determinations and their combined score (0-800) will be used to determine whether this factor is predictive of response to belinostat (by standard MRI criteria and/or by SRI defined previously in section 14.5) or overall outcome. Based on our preliminary results, the level of MIP expression will also be explored. This will be determined, when sufficient tissue is available for RNA extraction, by quantitative real-time PCR. Again, the level of MIP, as a continuous or discrete variable, will be assessed for its ability to predict for response to belinostat or overall outcome.

14.8 Interim analysis and stopping rule for efficacy/futility: While there will be stopping rules for toxicity/adverse events, *there will not be stopping rules for efficacy/futility.* The primary goal of the study is to determine whether early phase high resolution MRSI biomarkers can predict for improved PFS evaluated at 9 months after treatment initiation. Since our primary endpoint cannot be determined until 9 months after treatment and belinostat treatment will only be given in the last 45 patients enrolled, interim analyses for efficacy and futility is not applicable because we will not have enough subjects who have reached this endpoint in the middle of the study period.

15.0 DATA COLLECTION

15.1 Data submission forms: A copy of the eligibility/registration form will be submitted to the Emory Winship Cancer Institute Clinical Trial Office prior to initiating therapy.

- The clinical management system being used for this study is The Online Collaborative Research Environment (OnCore). OnCore will be used to record all study related information for all registered patients. All data must be entered no later than 30 days following each visit completion. All queries are to be resolved within 4 weeks of issue.

15.2 Submission of imaging and RT data: The imaging data will be collected with masked patient identification. All diagnostic imaging data sets will be electronically transferred to a secure server for visualization and analysis on the Velocity AI platform. In addition, patient treatment plans, including isodose clouds and all structure including tumor volumes and OARs, will be similarly transferred. For instructions on how to transfer each data set, please contact Edi Schriebmann at 404-778-5667. For MRSI, patient datasets will be transferred to a workstation where they can be post-processed and analyzed by the MIDAS software. The analyzed data will then be transferred, as above, in DICOM format into a secure server for analysis in Velocity AI.

15.3 Collaborating site: The Johns Hopkins University Hospital will be another site running this clinical study. They will be provided instructions to securely send their RT/MRI/MRSI data to Emory University for analysis. They should contact Edi Schriebmann at 404-778-5667 for more details on this procedure.

16.0 PATHOLOGY CONSIDERATIONS/SPECIMEN SUBMISSION

Molecular markers obtained as part of the standard clinical pathologic evaluation of GBMs at each institution will be assessed. These can (but may not necessarily) include the following: 1) EGFR amplification and PTEN status by FISH, 2) p53 status and isocitrate dehydrogenase 1 (IDH1) mutation status by immunohistochemistry (IHC), and 3) MGMT methylation status by methylation-specific PCR. In addition, paraffin blocks of tumor tissue will be required and evaluated by board-certified neuropathologists (Drs. Daniel Brat and Fausto Rodriguez) at the site where patients are enrolled. They

will pre-screen and select the block with at least 75% viable tumor. Unstained slides (10 slides/case) will be cut for use in immunohistochemistry and FISH and, if tissue is sufficient, for extraction of total RNA. All studies will be subsequently performed at Emory University. Unstained slides with corresponding H&E stained section from facility outside Emory (eg. Johns Hopkins) will be submitted to Dr. Hyunsuk Shim (404-778-4564) at 1701 Uppergate Drive, C5032, Bench 44, Winship Cancer Institute, Emory University, Atlanta, GA 30322, for further study within three months from study enrollment. After receipt of outside unstained slides, Dr. Shim will inform study coordinator who will log in receipt of materials into OnCore. After unstained slides are made and RNA extracted, the tissue block will be returned to the pathology department at the respective institution. To examine the histone acetylation status of the tumor, IHC staining with antibody specific for acetylated Histone H3 (Lys18) and H4 (Lys8) will be performed. The intensity of staining (brown color) is typically scored semi-quantitatively as follows: 1, weak/negative; 2, medium; 3, strong; and 4, very strong. An IHC score will be calculated by multiplying percentage of positive tumor cells (0-100) by staining intensity (1-4) producing a total range of 0–400 [86]. Two researchers will make independent determinations and their combined score (0-800) will be used to determine whether this factor is predictive of response to belinostat. The level of MIP expression will also be explored. This will be determined, when sufficient tissue is available for RNA extraction, by quantitative real-time PCR. Again, the level of MIP, as a continuous or discrete variable, will be assessed for its ability to predict for response to belinostat or overall outcome.

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Appendix 1

TMZ Medication Diary (Cycle 2-7 up to cycle 13, Cohorts 1 and 2)

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

Cycle No. ____ **TMZ daily dose** _____

Please record the time when temozolomide (TMZ) is taken. Days that do not apply will be marked out by coordinator.

Mon	**Tues**	**Wed**	**Thurs**	**Fri**	**Sat**	**Sun**
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____			

Research staff initials:_____ Date:_____

Comments:_____

_____

_____

TMZ Medication Diary (Cycle 1, Cohorts 1 & 2)

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

Cycle No. 1 **TMZ daily dose** _____

Please record the time when temozolomide (TMZ) is taken. Days that do not apply will be marked out by coordinator.

Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____
Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____	Date _____ TMZ _____

Research staff initials:_____ Date:_____

Comments:_____

_____

_____

Appendix 2 - Karnofsky Performance Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 3 – Neurocognitive Tests

NEUROCOGNITIVE TEST INSTRUCTIONS AND ADMINISTRATION PROCEDURES

1. Testing must be completed in one session. Test instructions must be followed verbatim with every patient at every study visit. All tests should be completed in black pen.
2. Tests should be administered in the following order to every patient and at every study visit: HVLT-R Part A (Learning Trials); Trail Making Test Part A; Trail Making Test Part B; COWAT; HVLT-R Part B (Delayed Recall); and the HVLT-R Part C (Delayed Recognition).
3. You may fill the delay interval between COWAT and HVLT-R Part B (Delayed Recall) with QOL questionnaires.
4. Patients should not be given copies of their tests to avoid learning the material between test administrations.

1. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

This test has three parts and six alternate forms:
Part A - Free Recall: Complete the three learning trials first
Part B - Delayed Recall: Complete after a 20 minute delay that includes administration of Trail Making Tests and COWAT as well as QOL assessments and symptom self-report measures, if appropriate
Part C - Delayed Recognition: Complete immediately after Delayed Recall

Part A – Free Recall: Trial 1

Examiner*: "I am going to read a list of words to you. Listen carefully, because when I am through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?"*

- Read the words at the rate of one word every 2 seconds.

***Examiner: "OK. Now tell me as many of those words as you can remember*."**

- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 2

Examiner*: "Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including the words you told me the first time."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, move on to trial 3. Later, you can record the number of words that were correctly repeated on the summary form.

Part A – Free Recall: Trial 3

Examiner*: "I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me."*

- Read the words at the rate of one word every 2 seconds.
- Check off the words the patient recalls on the form.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- Do not tell the respondent that recall of the words will be tested later.
- Record the time on the clock that you *complete* 'Part A – Free Recall' (for example, 10:00 am) on the designated space on the HVLT-R form.

2. TRAIL MAKING TEST [Timed Test]

Part A – Sample*:* The Sample for Part A must be completed/attempted by each patient and every assessment. Place the Sample A worksheet flat on the table, directly in front of the patient *(the bottom of the worksheet should be approximately six inches from the edge of the table).* Give the patient a black pen and say:

Examiner*: "On this page* (point) *are some numbers. Begin at number 1* (point to 1) *and draw a line from 1 to 2* (point to 2)*, 2 to 3* (point to 3)*, 3 to 4* (point to 4)*, and so on, in order, until you reach the end* (point to the circle marked END). *Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample A correctly and in a manner demonstrating that s/he understands what to do, proceed immediately to Test A. If the patient makes a mistake on Sample A, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***"This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 to 2, 2 to 3, and so on, until you reach the circle marked END"***

If it is clear that the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample A, take his/her hand and guide him/her through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Remember, begin at number 1 (*point to 1*) and draw a line from 1 to 2 (*point to 2*), 2 to 3 (*point to 3*), 3 to 4 (*point to 4*) and so on, in order, until you reach the circle marked END (*point*). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

If the patient does not succeed, or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part A – Test: After the patient has completed Sample A, place the Part A test worksheet directly in front of the patient and say:

Examiner*: "Good! Let's try the next one. On this page are numbers from 1 to 25. Do this the same way. Begin at number 1 (***point***) and draw a line from 1 to 2 (***point to 2***), 2 to 3 (***point to 3***), 3 to 4 (***point to 4***) and so on, in order, until you reach the circle marked END (***point***). Do not skip around, but go from one number to the next in proper order. Remember to work as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred
- The patient must complete the test in 3 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- If the patient does not complete the test within 3 minutes, terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Data Sheet indicating the reason the test was terminated and the last correct number reached on the test.
- If the patient successfully completes the test, collect the worksheet and record the time to completion on the Trail Making Data Sheet in minutes and seconds. Then say, ***"That's fine. Now we'll try another one."***

Part B – Sample: The Sample for Part B must be completed/attempted by each patient and every assessment. Place the Sample B worksheet flat on the table, directly in front of the patient (the bottom of the worksheet should be approximately six inches from the edge of the table) and say:

Examiner*: "On this page (***point***) are some numbers and letters. Begin at number 1 (***point to 1***) and draw a line from 1 to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***), 3 to C (***point to C***) and so on, in order, until you reach the end (***point to the circle marked END***). Remember, first you have a number (***point to 1***), then a letter (***point to A***), then a number (***point to 2***), then a letter (point to B), and so on. Draw the lines as fast as you can. Ready, begin."*

If the patient completes Sample B correctly, and in a manner demonstrating that s/he understands what to do, proceed immediately to Part B. If the patient makes a mistake on Sample B, point out the error and explain it. The following explanations of mistakes serve as illustrations:

- ***"You started with the wrong circle. This is where you start (point to number 1)"***
- ***"You skipped this circle (point to the circle omitted)"***
- ***"You should go from number 1 (***point***) to A (***point***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, until you reach the circle marked END (***point***)"***

If it is clear the patient intended to touch a circle but missed it, do not count it as an omission. Remind the patient, however, to be sure to touch the circles. If the patient still cannot complete Sample B, take their hand and guide them through the trail using the opposite end of the pen, lightly touching the worksheet to avoid making marks on the copy. Then say:

Examiner*: "Now you try it. Remember, begin at number 1 (***point to 1***) and draw a line from 1 to A (***point to A***), A to 2 (***point to 2***), 2 to B (***point to B***), B to 3 (***point to 3***) and so on, in order, until you reach the circle marked END (***point***). Ready, begin."*

If the patient does not succeed or it becomes evident that s/he cannot do the task, DISCONTINUE testing and indicate the corresponding reason on the Trail Making Test Data Sheet. If the patient completes Sample A correctly and appears to understand what to do, proceed immediately to Part A.

Part B – Test:
After the patient has completed Sample B, place the Part B Worksheet directly in front of the patient and say:

Examiner*: " Good! Let's try the next one. On this page are both numbers and letters. Do this the same way. Begin at number 1 (*point*) and draw a line from 1 to A (*point to A*), A to 2 (*point to 2*), 2 to B (*point to B*), B to 3 (*point to 3*), 3 to C (*point to C*) and so on, in order, until you reach the circle marked END (*point*). Remember, first you have a number (*point to 1*), then a letter (*point to A*), then a number (*point to 2*), then a letter (*point to B*), and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready, begin."*

- Start timing as soon as the instruction is given to "begin"
- Watch closely in order to catch any errors as soon as they are made. If the patient makes an error, call it to his/her attention immediately and have him/her proceed from the point the mistake occurred - do NOT start from the beginning
- The patient must complete the test in 5 minutes or less
- DO NOT STOP TIMING UNTIL HE/SHE REACHES THE CIRCLE MARKED "END"
- Collect the worksheet and record the time to completion on the Trail Making Test Data Sheet in minutes and seconds
- If the patient does not complete the test within 5 minutes, terminate the testing. The test can also be discontinued if the patient is extremely confused and is unable to perform the task. Collect the worksheet and complete the Trail Making Test Data Sheet indicating the reason the test was terminated and the last correct number or letter reached on the test.
- At the top of both Sample forms and both Test forms please write: subject ID number, date of evaluation, institution name, name of certified tester, and the certified tester's phone number.

3. CONTROLLED ORAL WORD ASSOCIATION TEST (COWAT) [Timed Test]
This test has three parts (letters) and two alternate forms.

Examiner*: "I am going to say a letter of the alphabet, and I want you to say as quickly as you can all of the words that you can think of that begin with that letter. You may say any words at all, except proper names such as the names of people or places. So you would not say 'Rochester' or 'Robert'. Also, do not use the same word again with a different ending, such as 'Eat,' and 'Eating.'*

"For example, if I say 's,' you could say 'son', 'sit,' 'shoe,' or 'slow.' Can you think of other words beginning with the letter 's'?"

Wait for the patient to give a word. If it is a correct response, say ***"good"***, and ask for another word beginning with the letter "s". If a second appropriate word is given, proceed to the test itself.

If the patient gives an inappropriate word on either occasion, correct the patient, and repeat the instructions. If the patient then succeeds, proceed to the test.

If the patient fails to respond, repeat the instructions. If it becomes clear that the patient does not understand the instructions or cannot associate, stop the procedure, and indicate the reason(s) on the scoring sheet and the Neurocognitive Evaluation Summary Form (CS).

If the patient has succeeded in giving two appropriate words beginning with the demonstration letter, say:

Examiner*: "That is fine. Now I am going to give you another letter and again you say all of the words beginning with that letter that you can think of. Remember, no names of people or places, just ordinary words. Also, if you should draw a blank, I want you to keep on trying until the time limit is up and I say STOP."*

"You will have a minute for each letter. The first letter is '___'" (see scoring sheet).

Allow exactly one minute for each letter

- If the patient discontinues before the end of the time period, encourage him/her to try to think of more words.
- If he/she is silent for 15 seconds, repeat the basic instruction and the letter (e.g., **"Tell me all the words you can think of that begin with a "c"**).
- No extension on the time limit is made in the event that instructions are repeated.
- Continue the evaluation with the remaining two letters, allowing one minute for each.

Recording and Scoring:

- The record sheet provides lines on which the patient's responses can be entered *(e.g., write in the word that is said by the patient)*. Record all patient responses verbatim. If his/her speed of word production is too fast to permit verbatim recording, a "+" should be entered to indicate a correct response.
- Incorrect responses should be struck through with a line and then initial and date in the margin next to the error.
- If the patient provides more responses than there are lines on the record sheet, place check marks in the boxes to indicate correct responses only.
- Count all the correct responses. The number of correct words should be indicated below each column on the recording sheet and on the Neurocognitive Evaluation Summary Form (CS) that is sent to the RTOG.

Comments on scoring:

- Note: It can be helpful for the first several patients and for patients known to be fast with their word production to tape record the session for transcription at a later time.
- The instructions include a specific prohibition against giving proper names or different forms of the same word. Therefore, inflections of the same word *(e.g., eat-eating; mouse-mice; loose-loosely; ran-run-runs)* are not considered correct responses.
- Patients often give both a verb and a word derived from the verb or adjective *(e.g., fun-funny; sad-sadness)*. These are not considered correct responses. On the other hand, if the word refers to a specific object *(e.g., foot-footstool; hang-hanger),* it would be counted as a correct answer.
- Many words have two or more meanings *(e.g., foot; can; catch; hand)*. A repetition of the word is acceptable IF the patient definitely indicates the alternative meaning to you.
- Slang terms are OK if they are in general use.

- Foreign words *(for example, pasta; passé; lasagna)* can be counted as correct if they can be considered part of the lexicon of the relevant language, the criterion being their listing in a standard dictionary of that language. All incorrect and repeated responses MUST be crossed out with one single line, initialed and dated. Additionally, all duplicate entries that have been verified to have different meanings must be marked "ok", initialed and dated. Refer to the descriptions above for guidelines for acceptability. Add the total number of correct responses in each column and input the totals where indicated on the COWAT worksheet.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Neurocognitive Evaluation Summary Form (CS)

4. HOPKINS VERBAL LEARNING TEST - REVISED (HVLT-R)

Part B – Delayed Recall

- ***DO NOT READ THE WORD LIST AGAIN.***
- Record the time on the clock that you *start* 'Part B – Delayed Recall' (for example, 10:20 am) on the designated space on the HVLT-R form.
- Administer 'Part B – Delayed Recall' after completing all Trail Making Tests and the COWAT. There should be at least 20 minutes between 'Part A' and 'Part B' of the HVLT-R. If the time is too short, allow the patients to complete a questionnaire.

Examiner: "*Do you remember that list of words you tried to learn before? Tell me as many of those words as you can remember."*

- Check the box on the corresponding line of the HVLT-R worksheet for each word the patient accurately recalls.
- If a word is said that is not in the list (*for example, "intrusion"*), do not write that word on the form and say nothing to the patient about the word not being on the list.
- There is no time limit for each recall trial. However, if the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words.
- If not, record the number of words that were correctly recalled on the summary form.

Part C – Delayed Recognition

Examiner*: "Now I'm going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No" if it was not. Was [word] on the list?"*

- Read the words from the top of the columns down.
- Check either the "**Y"** (Yes) or "**N"** (No) box next to each word to indicate the patient's response.
- Guessing is allowed.
- If the test is discontinued or omitted, please mark this on the bottom of the test form and indicate the reason on the Neurocognitive Evaluation Summary Form (CS).
- The score for this portion of the HVLT-R is the number of list words (i.e., words that in CAPS) correctly identified ("yes" response) minus the number of non-list words (i.e., words in lower case) incorrectly identified ("yes" response). Therefore, the actual score can range from –12 *(no list words identified and all non-list words identified)* to +12 *(all list words identified and no non-list words identified)*.

Appendix 4

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

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Date: ☐☐ / ☐☐ / ☐☐ (month) / (day) / (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: ☐☐☐

MD Anderson # : ☐☐☐☐☐☐

PDMS # : ☐☐☐☐

M. D. Anderson Symptom Inventory - Brain Tumor (MDASI - BT)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been in the last 24 hours. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
14. Your **weakness** on one side of the body at its WORST?	○	○	○	○	○	○	○	○	○	○	○
15. Your difficulty **understanding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
16. Your difficulty **speaking** (finding the words) at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

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Date: ☐☐ / ☐☐ / ☐☐ (month) (day) (year)

Study Name: _____
Protocol #: _____
PI: _____

Subject Initials: _____

MD Anderson #: ☐☐☐☐☐☐ **PDMS #:** ☐☐☐☐

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
17. Your **seizures** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your difficulty **concentrating** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **vision** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
20. Your change in **appearance** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
21. Your change in **bowel pattern** (diarrhea or constipation) at its WORST?	○	○	○	○	○	○	○	○	○	○	○
22. Your **irritability** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

SAMPLE

Part II. How have your symptoms interfered with your li

Symptoms frequently interfere with h[illegible] we[illegible] function. How much have your symptoms interfered with the following items in the last 24 [illegible]:

	Did not interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
23. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
24. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
25. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
26. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
27. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
28. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

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Appendix 5

INVENTORY OF DEPRESSIVE SYMPTOMATOLOGY (SELF-REPORT)
(IDS-SR)

NAME: _____ TODAY'S DATE _____

Please circle the one response to each item that best describes you for the past seven days.

1. Falling Asleep:
   - 0 I never take longer than 30 minutes to fall asleep.
   - 1 I take at least 30 minutes to fall asleep, less than half the time.
   - 2 I take at least 30 minutes to fall asleep, more than half the time.
   - 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:
   - 0 I do not wake up at night.
   - 1 I have a restless, light sleep with a few brief awakenings each night.
   - 2 I wake up at least once a night, but I go back to sleep easily.
   - 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:
   - 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
   - 1 More than half the time, I awaken more than 30 minutes before I need to get up.
   - 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
   - 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:
   - 0 I sleep no longer than 7-8 hours/night, without napping during the day.
   - 1 I sleep no longer than 10 hours in a 24-hour period including naps.
   - 2 I sleep no longer than 12 hours in a 24-hour period including naps.
   - 3 I sleep longer than 12 hours in a 24-hour period including naps.

5. Feeling Sad:
   - 0 I do not feel sad
   - 1 I feel sad less than half the time.
   - 2 I feel sad more than half the time.
   - 3 I feel sad nearly all of the time.

6. Feeling Irritable:
   - 0 I do not feel irritable.
   - 1 I feel irritable less than half the time.
   - 2 I feel irritable more than half the time.
   - 3 I feel extremely irritable nearly all of the time.

7. Feeling Anxious or Tense:
   - 0 I do not feel anxious or tense.
   - 1 I feel anxious (tense) less than half the time.
   - 2 I feel anxious (tense) more than half the time.
   - 3 I feel extremely anxious (tense) nearly all of the time.

8. Response of Your Mood to Good or Desired Events:
   - 0 My mood brightens to a normal level which lasts for several hours when good events occur.
   - 1 My mood brightens but I do not feel like my normal self when good events occur.
   - 2 My mood brightens only somewhat to a rather limited range of desired events.
   - 3 My mood does not brighten at all, even when very good or desired events occur in my life.

9. Mood in Relation to the Time of Day:
   - 0 There is no regular relationship between my mood and the time of day.
   - 1 My mood often relates to the time of day because of environmental events (e.g., being alone, working).
   - 2 In general, my mood is more related to the time of day than to environmental events.
   - 3 My mood is clearly and predictably better or worse at a particular time each day.

   9A. Is your mood typically worse in the morning, afternoon or night? (circle one)

   9B. Is your mood variation attributed to the environment? (yes or no) (circle one)

10. The Quality of Your Mood:
    - 0 The mood (internal feelings) that I experience is very much a normal mood.
    - 1 My mood is sad, but this sadness is pretty much like the sad mood I would feel if someone close to me died or left.
    - 2 My mood is sad, but this sadness has a rather different quality to it than the sadness I would feel if someone close to me died or left.
    - 3 My mood is sad, but this sadness is different from the type of sadness associated with grief or loss.

Please complete either 11 or 12 (not both)

11. Decreased Appetite:

0 There is no change in my usual appetite.
1 I eat somewhat less often or lesser amounts of food than usual.
2 I eat much less than usual and only with personal effort.
3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

12. Increased Appetite:

0 There is no change from my usual appetite.
1 I feel a need to eat more frequently than usual.
2 I regularly eat more often and/or greater amounts of food than usual.
3 I feel driven to overeat both at mealtime and between meals.

Please complete either 13 or 14 (not both)

13. Decreased Weight (Within the Last Two Weeks):

0 I have not had a change in my weight.
1 I feel as if I've had a slight weight loss.
2 I have lost 2 pounds or more.
3 I have lost 5 pounds or more.

14. Increased Weight (Within the Last Two Weeks):

0 I have not had a change in my weight.
1 I feel as if I've had a slight weight gain.
2 I have gained 2 pounds or more.
3 I have gained 5 pounds or more.

15. Concentration/Decision Making:

0 There is no change in my usual capacity to concentrate or make decisions.
1 I occasionally feel indecisive or find that my attention wanders.
2 Most of the time, I struggle to focus my attention or to make decisions.
3 I cannot concentrate well enough to read or cannot make even minor decisions.

16. View of Myself:

0 I see myself as equally worthwhile and deserving as other people.
1 I am more self-blaming than usual.
2 I largely believe that I cause problems for others.
3 I think almost constantly about major and minor defects in myself.

17. View of My Future:

0 I have an optimistic view of my future.
1 I am occasionally pessimistic about my future, but for the most part I believe things will get better.
2 I'm pretty certain that my immediate future (1-2 months) does not hold much promise of good things for me.
3 I see no hope of anything good happening to me anytime in the future.

18. Thoughts of Death or Suicide:

0 I do not think of suicide or death.
1 I feel that life is empty or wonder if it's worth living.
2 I think of suicide or death several times a week for several minutes.
3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

19. General Interest:

0 There is no change from usual in how interested I am in other people or activities.
1 I notice that I am less interested in people or activities.
2 I find I have interest in only one or two of my formerly pursued activities.
3 I have virtually no interest in formerly pursued activities.

20. Energy Level:

0 There is no change in my usual level of energy.
1 I get tired more easily than usual.
2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking or going to work).
3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

21. Capacity for Pleasure or Enjoyment (excluding sex):

0 I enjoy pleasurable activities just as much as usual.
1 I do not feel my usual sense of enjoyment from pleasurable activities.
2 I rarely get a feeling of pleasure from any activity.
3 I am unable to get any pleasure or enjoyment from anything.

22. Interest in Sex (Please Rate Interest, not Activity):

    0 I'm just as interested in sex as usual.
    1 My interest in sex is somewhat less than usual or I do not get the same pleasure from sex as I used to.
    2 I have little desire for or rarely derive pleasure from sex.
    3 I have absolutely no interest in or derive no pleasure from sex.

23. Feeling slowed down:

    0 I think, speak, and move at my usual rate of speed.
    1 I find that my thinking is slowed down or my voice sounds dull or flat.
    2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.
    3 I am often unable to respond to questions without extreme effort.

24. Feeling restless:

    0 I do not feel restless.
    1 I'm often fidgety, wring my hands, or need to shift how I am sitting.
    2 I have impulses to move about and am quite restless.
    3 At times, I am unable to stay seated and need to pace around.

25. Aches and pains:

    0 I don't have any feeling of heaviness in my arms or legs and don't have any aches or pains.
    1 Sometimes I get headaches or pains in my stomach, back or joints but these pains are only sometime present and they don't stop me from doing what I need to do.
    2 I have these sorts of pains most of the time.
    3 These pains are so bad they force me to stop what I am doing.

26. Other bodily symptoms:

    0 I don't have any of these symptoms: heart pounding fast, blurred vision, sweating, hot and cold flashes, chest pain, heart turning over in my chest, ringing in my ears, or shaking.
    1 I have some of these symptoms but they are mild and are present only sometimes.
    2 I have several of these symptoms and they bother me quite a bit.
    3 I have several of these symptoms and when they occur I have to stop doing whatever I am doing.

27. Panic/Phobic symptoms:

    0 I have no spells of panic or specific fears (phobia) (such as animals or heights).
    1 I have mild panic episodes or fears that do not usually change my behavior or stop me from functioning.
    2 I have significant panic episodes or fears that force me to change my behavior but do not stop me from functioning.
    3 I have panic episodes at least once a week or severe fears that stop me from carrying on my daily activities.

28. Constipation/diarrhea:

    0 There is no change in my usual bowel habits.
    1 I have intermittent constipation or diarrhea which is mild.
    2 I have diarrhea or constipation most of the time but it does not interfere with my day-to-day functioning.
    3 I have constipation or diarrhea for which I take medicine or which interferes with my day-to-day activities.

29. Interpersonal Sensitivity:

    0 I have not felt easily rejected, slighted, criticized or hurt by others at all.
    1 I have occasionally felt rejected, slighted, criticized or hurt by others.
    2 I have often felt rejected, slighted, criticized or hurt by others, but these feelings have had only slight effects on my relationships or work.
    3 I have often felt rejected, slighted, criticized or hurt by others and these feelings have impaired my relationships and work.

30. Leaden Paralysis/Physical Energy:

    0 I have not experienced the physical sensation of feeling weighted down and without physical energy.
    1 I have occasionally experienced periods of feeling physically weighted down and without physical energy, but without a negative effect on work, school, or activity level.
    2 I feel physically weighted down (without physical energy) more than half the time.
    3 I feel physically weighted down (without physical energy) most of the time, several hours per day, several days per week.

Which 3 items (questions) were the easiest to understand? _____

Thank you

Range 0-84 Score: _____

Appendix 6.

4 wks after
Cycle 7

Timing of assessments

belinostat only (cohort 2)

Diagnostic MRI MRSI &IDS-SR Neurocognitive & QOL

Neurocognitive & QOL – Perform every 6 months after therapy is complete up to 2 years post-RT if no tumor progression. If tumor progresses within 2 years post-RT, last assessment will be performed at progression.

Diagnostic MRI – Perform every 3 months after therapy is complete up to 2 years post-RT. Subsequent MRI followup will be at the discretion of treating physicians.

