A Randomized Feasibility Study Evaluating Temozolomide Chronotherapy for High Grade Glioma

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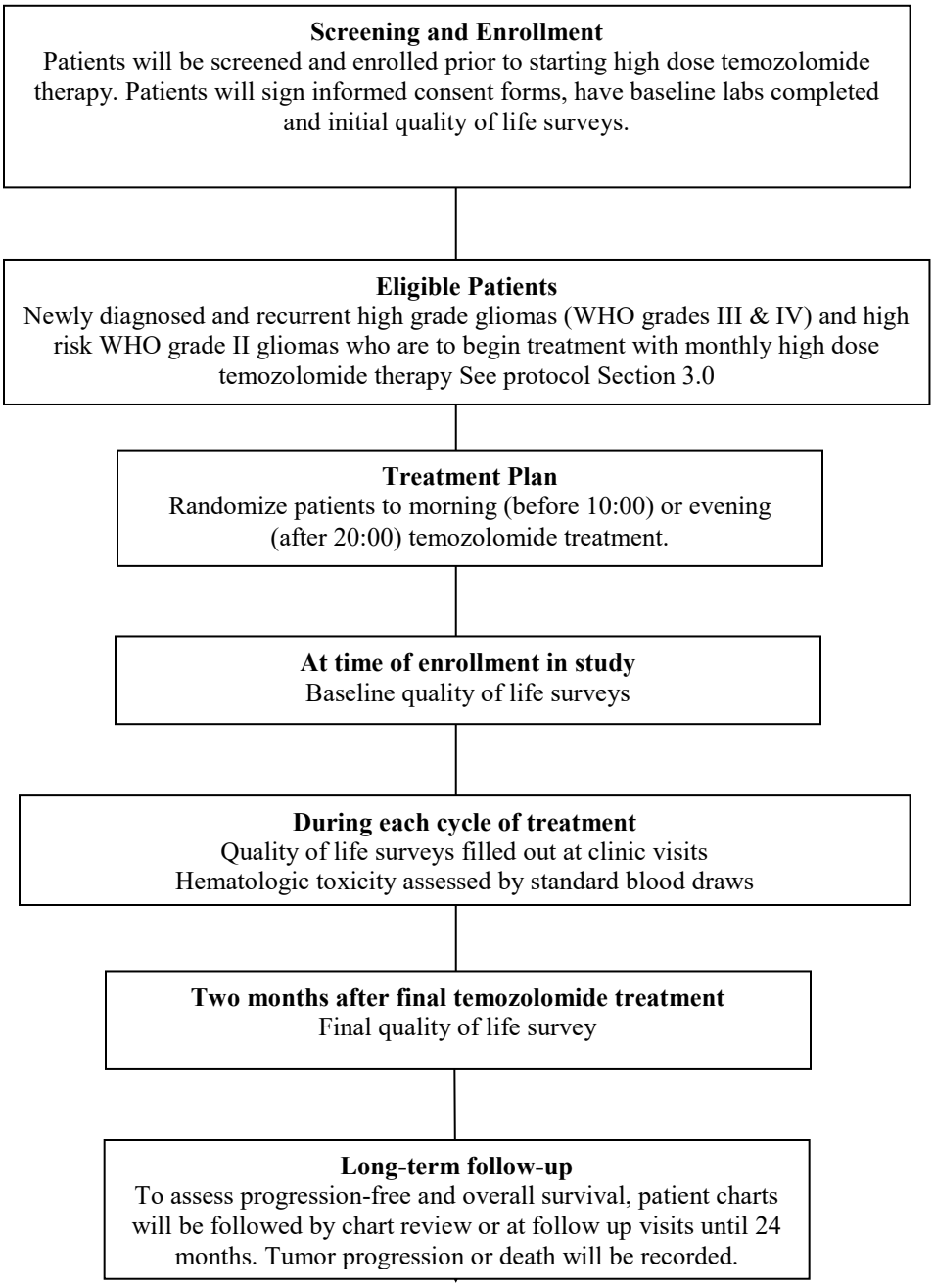
SCHEMA



Glossary of Abbreviations

AE	Adverse event
CBV	Cerebral Blood Volume
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DOB	Date of Birth
DSM	Data and Safety Monitoring
HRPO	Human Research Protection Office (IRB)
HGG	High Grade Glioma
IRB	Institutional Review Board
MD	Medical Doctor
MLA	Minimal lumen area
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression Free Survival
PI	Principal investigator
PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee
QOL	Quality of Life
RANO	Response Assessment in Neuro-Oncology
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
T2/FLAIR	T2-weighted Fluid Attenuated Inversion Recovery
TEAE	Treatment-emergent adverse events
TMZ	Temozolomide
UPN	Unique patient number
WHO	World Health Organization

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1.0 BACKGROUND AND RATIONALE

1.1 Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is the most aggressive and most common malignant primary brain tumor in adults (Ostrom et al., 2013). GBM accounts for 15.6% of all primary brain and central nervous system (CNS) tumors and 54.4% of all gliomas (Ostrom et al., 2013; Central Brain Tumor Registry of the United States) (Figure 1).

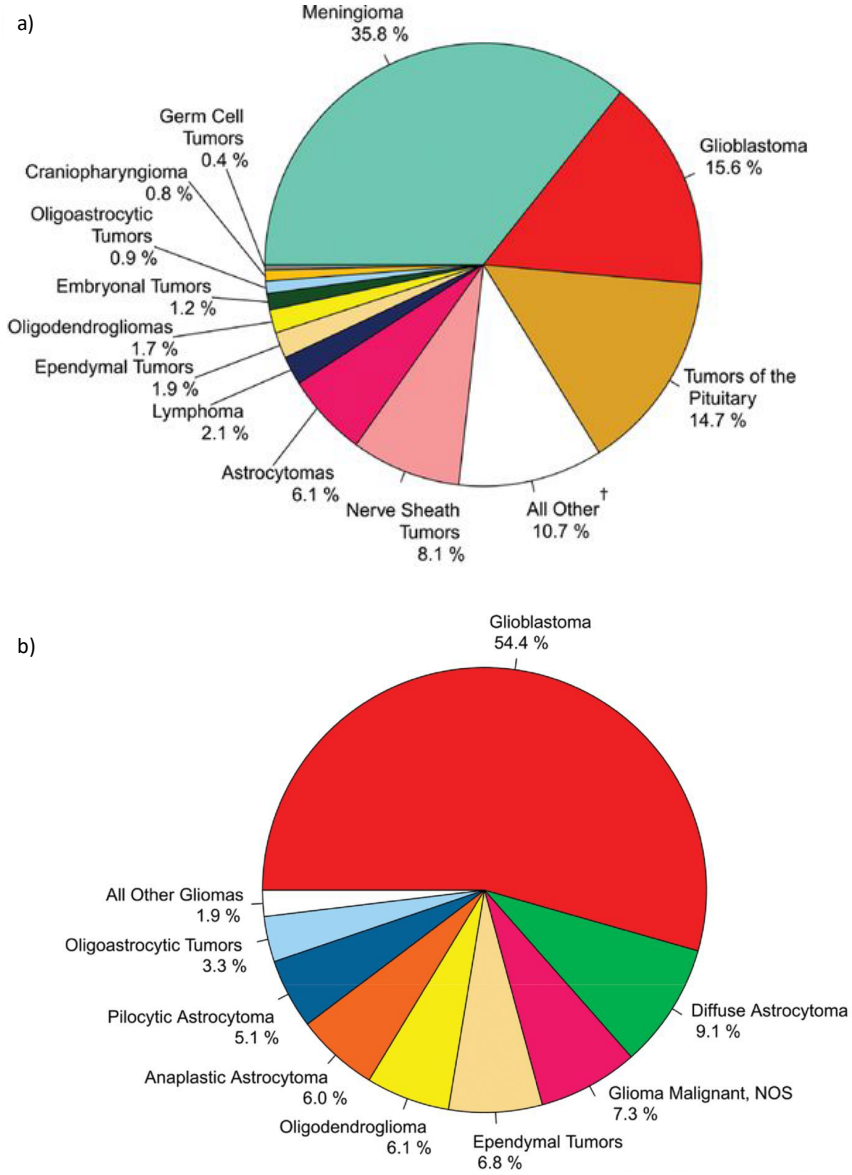

Figure 1. Distribution of primary brain and CNS tumors. (a) Distribution of primary and CNS based on histology. (b) Distribution of primary brain and CNS gliomas based on histology. Ostrom et al., 2013, modified.

Standard therapy for treatment of GBM includes surgical resection followed by radiation

therapy with concomitant temozolomide.

1.2 Temozolomide (Temodar)

The addition of the DNA alkylator temozolomide extended median survival by 2.5 months compared to surgical resection and radiation therapy alone (Stupp et al., 2005; figure 2).

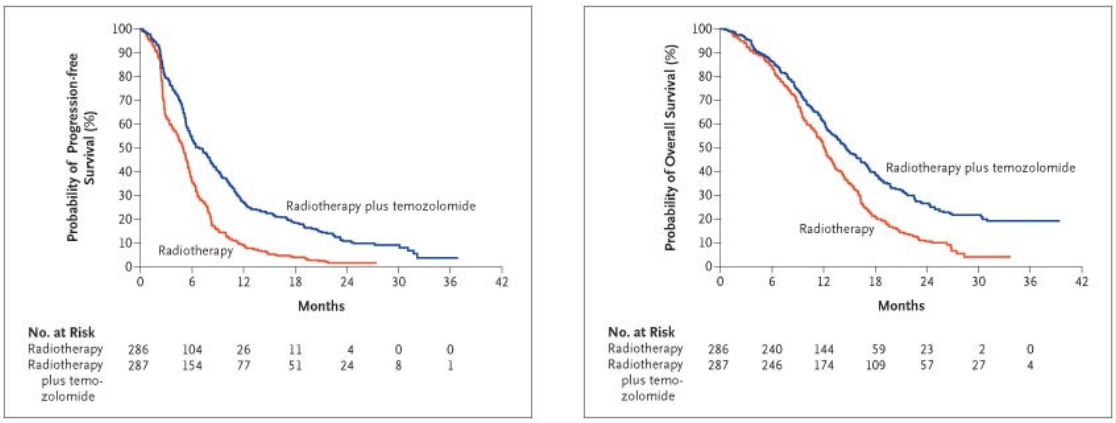

Figure 2. Progression-free survival (PFS) (left) and overall survival (OS) (right) of GBM patients receiving radiotherapy plus temozolomide versus radiotherapy alone. (Stupp et al, 2005, modified).

Despite initial response to standard therapy, GBM has a poor prognosis, resulting in a median survival of 14.6 months (Ohka et al., 2012). Development of new therapies is important, but equally important is the optimization of currently available therapies for patients who are fighting to survive brain tumors now.

1.3 Chronotherapy

Chronotherapy is the improvement of treatment outcomes by minimizing treatment toxicity and maximizing efficacy through delivery of a medication according to the timing of biological rhythms within a patient (Levi and Okyar, 2011). This concept has been applied to a variety of medications, including chemotherapeutics. Chronochemotherapy has successfully improved anti-tumor effect in the treatment of metastatic colon cancer (Levi et al., 1995, 2001; Innominato et al., 2010), improved survival rate in patients with ovarian cancer (Kobayashi et al., 2002), and decreased relapse rate for children with acute lymphoblastic leukemia (Rivard et al., 1993; Schmeigelow et al., 1997). Chronotherapy has the capacity to improve treatment outcomes for many other cancers, including GBM.

In a mouse model of GBM, we have demonstrated greater anti-tumor efficacy of temozolomide during morning administration. Delivery of temozolomide by oral gavage at 7am showed a trend toward increased length of survival compared to delivery at 7pm (Figure 3).

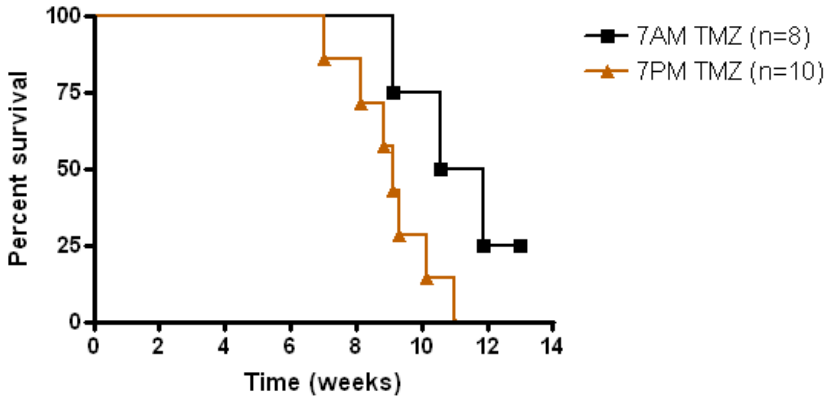

Figure 3. Morning temozolomide (TMZ) treatment lengthens survival. Delivery of TMZ at 7am resulted in a longer median survival than 7pm TMZ delivery (11.2 vs 9.1 weeks, p=0.057).

In a follow-up study with decreased tumor burden, intracranial GBM tumors shrank at a greater rate following 7am TMZ treatment compared to 7pm TMZ treatment. Tumor size was determined based upon weekly measurement of a bioluminescent reporter expressed by tumor cells. Figure 4 demonstrates a reduction in average tumor size for mice receiving TMZ. Mice receiving vehicle have continued tumor growth.

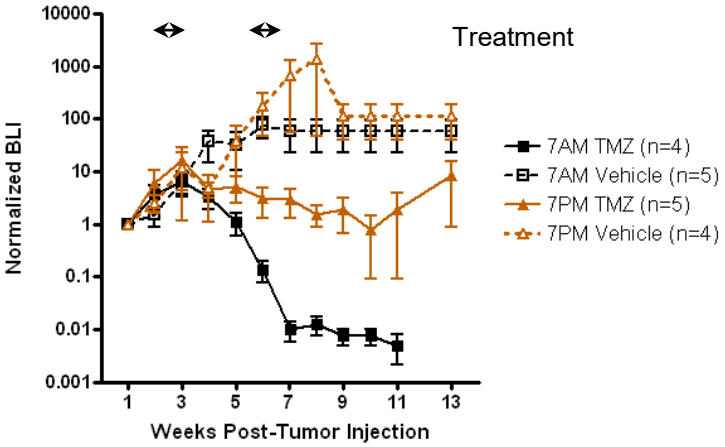

Figure 4. Morning TMZ treatment results in greater reduction in tumor size compared to evening TMZ treatment.

1.4 Circadian Clock

For decades, scientists have studied the regulation of daily oscillations in biological processes. At the end of the twentieth century, a regulator of these daily oscillations was discovered within individual cells, known as the molecular clock. Core clock genes form a molecular clock within cells to regulate a variety of cellular processes through the transcriptional control of gene expression (Reppert & Weaver, 2002). Reduced expression of several core clock genes, including Period2 and Period3, has been correlated with decreased survival in glioma patients (Repository for Molecular Brain Neoplasia Data, Figure 5).

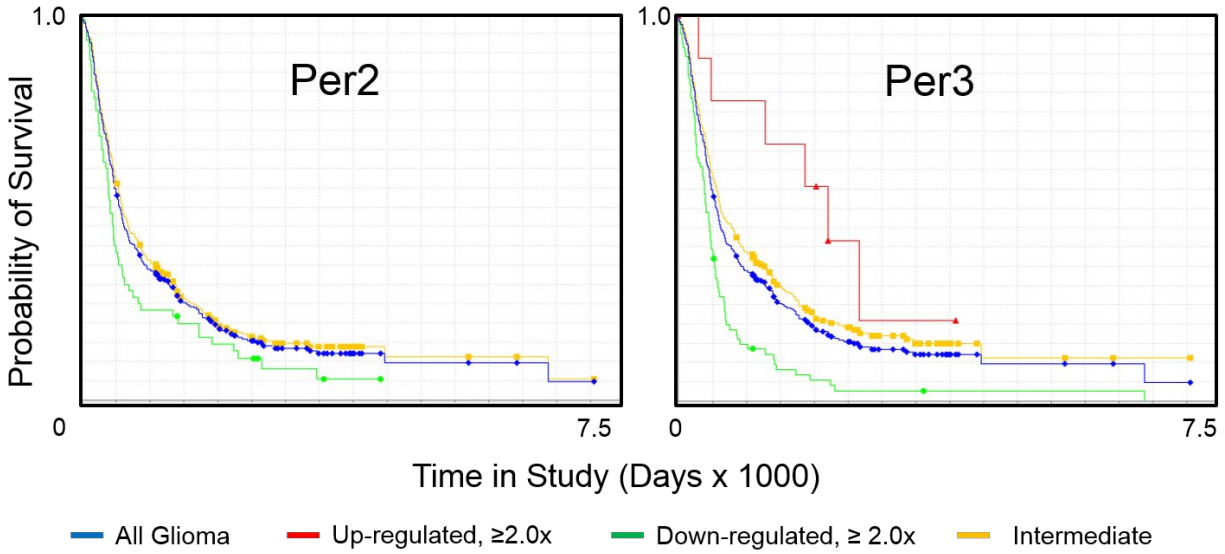

Figure 5. Decreased survival is correlated with reduced core clock gene expression in gliomas. Downregulated expression of core clock genes Period2 and Period3 is linked to decreased survival in 343 glioma patients (Repository for Molecular Brain Neoplasia Data).

The molecular clock has also been linked to the DNA damage response pathway through protein-protein interactions of Period1 and Period3 with ATM, enhancing downstream phosphorylation of Chk2 in response to DNA double strand breaks (Figure 6; Gery et al., 2006; Im et al., 2010). These discoveries suggest a role for the molecular clock in the cellular response to DNA damage. Therefore, DNA damaging agents like temozolomide may be most effective at the time when core clock proteins Period1 and Period3 are most abundant in the cell.

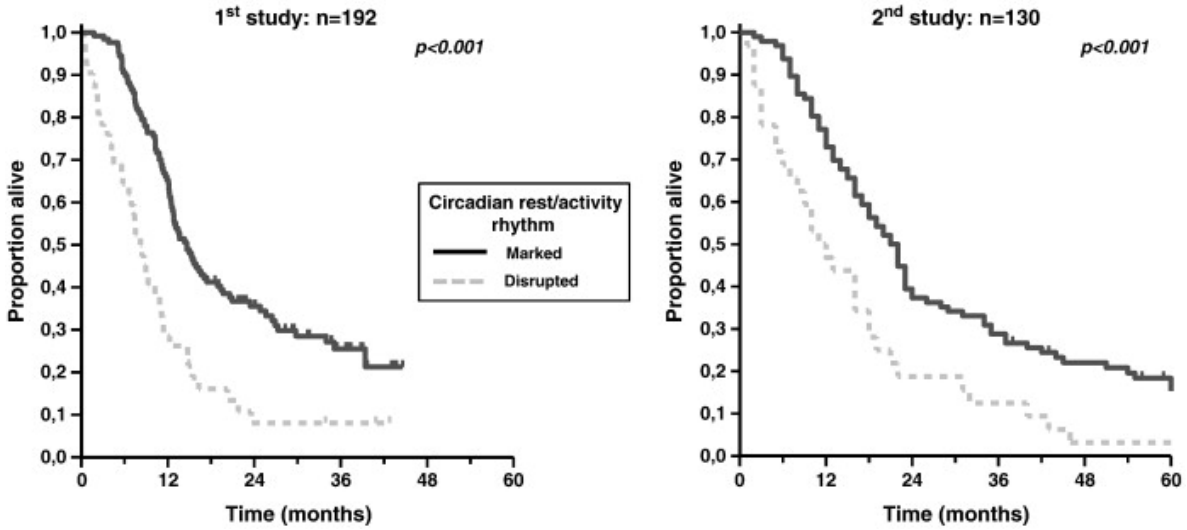

Figure 6. Survival curves of patients with metastatic colorectal cancer according to the presence or absence of circadian disruption before chemotherapy start. The locomotor rhythm, recorded by a wrist-actigraph, was used as circadian biomarker. Circadian disruption was defined as being present in patients whose dichotomy index was in the lowest quartile (dashed grey line). The left panel shows data from 192 patients, receiving chronomodulated chemotherapy, as first or second line treatment. The right panel shows data from 130

previously untreated patients receiving either chronomodulated or conventional chemotherapy. (from Innominato et al, ADDR 2010).

1.5 Anti-Tumor T Cell Activity and Circadian Rhythms

The immune response is an important predictor of glioma progression. Generally, the immune system and, more specifically, T lymphocytes are known to recognize tumor cells and target them for destruction. This action can initially restrain solid tumor growth. In support of this concept, glioma patients with lymphopenia have worse OS (Grossman et al, 2011). Chemotherapy such as TMZ that targets highly proliferative populations affects T cell populations in addition to tumor cells. T lymphocyte populations experience rapid proliferation, especially after exposure to activating antigen, like that released when a tumor cells dies from chemotherapy. However, the rapid proliferation of the T lymphocytes could be inhibited by chemotherapy. Glioma patients given TMZ and radiation experience lymphopenia after two months of treatment and lymphocyte counts remain depressed during the entire course of treatment (Grossman et al 2011). It would be ideal to specifically target the tumor cells while allowing the anti-tumor T cells to remain.

Like many other processes in the body, lymphocyte proliferation is dependent on circadian rhythms. Multiple studies have shown differential effects on lymphopenia depending on the time of day chemotherapy is administered. In a retrospective study, gemcitabine given at 9:00 am was less toxic to lymphocytes than gemcitabine given at 3:00 pm (Iwata K et al, 2011). In other studies, T cell progenitors in the bone marrow were found to be less proliferative at night. Due to the reduced proliferation, nighttime administration of docetaxel and irinotecan was found to reduce lymphocyte toxicity (Tampellini M et al 1998, Ohdo S 1997). This would suggest administering chemotherapy at a time of less T cell proliferation would prevent lymphopenia and potentially support the T cell mediated anti-tumor immune response as well as allow patients to stay on treatment schedule. This could be an addition mechanism by which patients could benefit from chronotherapy.

1.6 Quality of Life

Beyond patient outcome and measured biologic outcomes, it is also important to consider patient quality of life in response to treatment. Quality of life refers to the patient's ability to conduct themselves as normal in reference to physical well-being, social interactions, emotional well-being, and ability to function normally. These qualities can be assessed through surveys administered to the patient throughout their disease and treatment (Piil et al 2015, Omuro et al 2014). Side effects and disease progression can influence quality of life significantly. In this study we will assess quality of life to determine how chronotherapy increases quality life experienced by some patients.

1.7 Study Rationale

Temozolomide (TMZ) is the chemotherapy drug approved by the FDA to increase survival in glioblastoma (GBM) patients beyond surgical resection and radiation therapy alone. Give its activity in astrocytomas, TMZ is commonly used in grade III anaplastic astrocytoma (AA) as well. Both grade III AA and grade IV GBM are high grade gliomas

(HGG). The short half-life of this drug and known oscillations in DNA damage repair make it an ideal candidate for chronotherapy. Chronotherapy has improved outcomes through the reduction of side effects and increase in anti-tumor activity for a variety of cancers, but has never been applied to the treatment of gliomas. Based on the preliminary preclinical data for chronotherapeutic TMZ treatment of intracranial glioma xenografts and the success of chronotherapy in the treatment of other cancers, we hypothesize that the timing of TMZ treatment will alter its efficacy and toxicity.

These effects will be assessed by the following means:

1. Randomized assignment of patients to one of two treatment time frames (before 10:00 versus after 20:00).
2. Measurement of hematologic toxicity throughout treatment.
3. Assessment of QOL through surveys.
4. Correlation of PFS and OS to chronotherapeutic treatment windows.
5. Assessment of daily rest-activity rhythms as well as overall daily activity.

2.0 OBJECTIVES

This exploratory study will collect pilot data for assessment of treatment outcomes in future glioma chronotherapeutic studies.

2.1 Primary Objective

To determine the feasibility of treatment compliance and randomization of HGG patients to receive temozolomide between morning (before 10:00) or evening (after 20:00) treatment groups. Feasibility is defined as at least 80% compliance with assigned administration time.

2.2 Secondary Objectives

1. To determine the number of HGG patients with grade 3 or 4 hematologic toxicity, including lymphopenia, thrombocytopenia, neutropenia and anemia, while receiving temozolomide when administered in the morning (before10:00) or evening (after 20:00).
2. To assess quality of life using quality of life surveys in HGG patients receiving temozolomide in the morning versus evening.
3. To evaluate progression-free survival of HGG patients taking TMZ in the morning versus evening through chart view or patient visits.
4. To determine overall survival of HGG patients taking TMZ in the morning versus evening through chart review or patient visits.
5. To correlate the sleep-wake cycles of patients receiving temozolomide for treatment of HGG with treatment outcomes for morning versus evening TMZ treatments.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. **Newly diagnosed and recurrent** high grade **gliomas (WHO grades III & IV) and high risk WHO grade II gliomas who are to begin treatment with monthly high dose temozolomide therapy.**

2. At least 18 years of age.

3. Karnofsky performance status ≥ 60%, see Appendix A

4. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry.

3.3 Inclusion of Minorities

Women and members of all races and ethnicities are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Randomization

Eligible patients will be randomized on a 1:1 basis to receive temozolomide at one of two time points: before 10:00 or after 20:00. A computer-generated randomization scheme is used to assign subjects. It is maintained centrally by the study statistician.

5.0 STUDY PLAN

5.1 Study Procedures

Temozolomide will be given as per standard of care. Typical dosing is 150 to 200 mg/m^2 on Days 1 through 5 of a 28-day treatment cycle. Patients will be randomized to take their temozolomide doses in the morning (before 10:00) or evening (after 20:00). Compliance with dosing times will be verified by means of a medication diary (Appendix B). Patients who miss taking their dose at the assigned time will be instructed to take the dose as soon as they can (as long as the next scheduled dose is at least 12 hours away) rather than omitting it.

Patients will be given an ActTrust Condor Instrument watch after signing the consent form. Patients will be required to wear the ActTrust Condor Instrument watch 24 hours per day; it should only be removed at specified data collection time points (see protocol calendar 9.0). Actimetry data will be collected at corresponding time points with the return of the patient to clinic every 8 weeks. The ActTrust watch does not require the patient to charge the device, thus the patient will never have to remove the watch and a new, fully charged, watch will be provided to the patient at every collection time point.

5.2 Study Assessments

5.2.1 Hematologic toxicity

Hematologic toxicity will be assessed by standard blood collection. Blood draws will occur within the same 4-hour window each cycle for each patient to take into account peripheral blood T cell numbers. (Timing of draws need not be

synchronized across patients, only consistent for each individual patient.)

Hematologic toxicity will include grade 3 and 4 lymphopenia, thrombocytopenia, anemia and neutropenia. The criteria are summarized in the following chart:

Toxicity	Cell Type	Grade III criteria	Grade IV criteria
Lymphopenia	Lymphocytes	<500-200/mm3	<200/mm3
Leukopenia	Leukocytes	<2000-1000/mm3	<1000/mm3
Neutropenia	Neutrophils	<1000-500/mm3	<500/mm3
Thrombocytopenia	Platelets	<50,000-25,000/mm3	<25,000/mm3
Anemia	RBC (Hemoglobin)	<8.0-6.5 g/dL	<6.5 g/dL

5.3 Duration of Study Participation

Patients will be considered active participants from time of consent through 2 months following the last cycle of temozolomide. Patients will be followed after this time for 24 months.

5.4 Definition of Evaluability

Patients receiving a minimum of one full cycles of TMZ will be evaluable for the primary endpoint.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Dose delays or dose modifications will follow the standard of care.

7.0 CORRELATIVE STUDIES

7.1 Quality of Life Surveys

Patient quality of life will be assessed using a standard quality of life survey specifically designed for brain cancer patients (the FACT-Br, see Appendix C). QOL assessments will be performed at the following time points:

- baseline
- at the beginning of each cycle of chemotherapy
- 1 month after the final chemotherapy treatment.

The QOL surveys will be administered during an office visit by the study coordinator.

7.2 Wrist Actimetry and Sleep Questionnaire

The ActTrust Condor Instrument watches are wrist actimetry/accelerometers. Large datasets from these devices can be accessed and analyzed through ActStudio (Condor Instruments). This technology has been used already by several groups at Washington University in St. Louis.

Patients will wear an accelerometer on their wrist to measure activity level during the day and at night until two months after the end of treatment. The accelerometer will appear similar to an athletic wristwatch. Patients will be required to wear the accelerometer at all times starting at the beginning of treatment or as soon as they are enrolled in the study, whichever is later. Patients will remove the accelerometer only during situations when the accelerometer would be completely submersed in water or liquid. Wrist actigraphy will be quantified in one-minute bins for the duration of the recording (typically 60 days per patient). The data (counts per minute) will be quantified in terms of average activity per day, percent of activity during waking, percent of activity during sleep, chronotype (average time of daily mid-sleep), chronotype variability (e.g. cycle-to-cycle standard deviation of daily chronotype), sleep duration, nap duration, and number of naps per day. This data will be collected once every 2 months. Patients will not need to charge the watch and upon data collection, a new watch (that is fully charged) will be available for them to take. Once data are collected, it will be analyzed for sleep/wake cycles and overall activity level. Total activity will be measured as average acceleration over 24 hours. Patterns of acceleration will also be noted relative to treatment times in 2 hour increments.

At baseline and at the beginning of each cycle of TMZ, the patient will complete a sleep questionnaire that will be used in conjunction with the ActTrust watch. This qualitative data (sleep questionnaire) will be used with the quantitative data (collected via the ActTrust watch) to assess the level of disruption in sleep/wake cycles experienced by the patient while on study. This data will be collected up to 1 month after the last TMZ treatment. These sleep questionnaires will be administered during an office visit by the study coordinator.

8.0 REGULATORY AND REPORTING REQUIREMENTS

The Principal Investigator is responsible for ensuring the safety of subjects who have enrolled in the study. The PI will monitor the study for adverse events directly attributable to participation in this study (i.e. events associated with the research specimen collections and QOLs, not events associated with routine administration of temozolomide). Because the care obtained while on trial is indicated and standard of care, no adverse events are likely to be attributable to enrollment. If any breach of confidentiality were to occur, it would be reported according to the HRPO-recommended guidelines.

9.0 STUDY CALENDAR

	Baseline	Beginning of each cycle of TMZ	1 month after the last TMZ treatment[3]	Follow-up[1]
Informed consent	X			
ActTrust Condor Instrument watch	Continuously beginning after the signing of consent but no more than 2 weeks prior to initiation of TMZ			
Sleep Questionnaire	X	X	X	
FACT-Br	X	X	X	
Randomization	X			
Tracking of hematologic toxicity[2]		X		
Review of medical record				X

1. Every 3 months by chart review looking for progression and survival.
2. From SOC blood draws.
3. To coincide with the patient's SOC end of treatment follow up visit with treating physician.

10.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form FACT-Br Randomization Form Quality of Sleep Questionnaire	Prior to starting treatment
Hematologic Toxicity Form	Monthly
Medication Diary	End of every cycle
FACT-Br Quality of Sleep Questionnaire	Beginning of each cycle 1 month after EOT
Follow-Up Form	Every 3 months until 24 months after active participation

11.0 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 +/- 1 weeks. After the first year, scans may go to every 12 weeks +/- 1 week. After the second year,

scans may go to every 16 weeks +/-1 week, depending on physician choice. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the updated response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology (RANO) working group guideline [JCO 28(11): 1963-1972, 2010].

Criteria for Determining First Progression Depending on Time from Initial Chemoradiotherapy

First Progression	Definition
Progressive disease < 12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (eg, solid tumor areas [ie, > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥ 12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥ 25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (eg, effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Criteria for Response Assessment Incorporating MRI and Clinical Factors (Adapted from JCO 2010)

Response	Criteria
Complete response	• Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks. • No new lesions; stable or improved nonenhancing (T2/FLAIR) lesions.

Response	Criteria
	• Patients must be off corticosteroids (or on physiologic replacement doses only) and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: • ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. • No progression of nonmeasurable disease. • Stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan. • Stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: • Does not qualify for complete response, partial response, or progression. • Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: • ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids*. The absolute increase in any dimension must be at least 5mm when calculating the products. • Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). • Any new measureable lesion. • Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose.

Response	Criteria
	• Failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

- NOTE. All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
- Stable doses of corticosteroids include patients not on corticosteroids.

11.2 Disease Parameters

Measurable disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable or evaluable disease: Uni-dimensionally measurable lesions or lesions with margins not clearly defined such as areas of T2/FLAIR signal abnormality or poorly defined enhancing abnormality.

Note: For cystic lesions, the only measurable part is any enhancement area around the cyst that is clearly defined and bi-dimensionally measurable. The cyst itself should not be considered measurable or non-measureable disease.

Target lesions: All measurable lesions that are residual of the lesion treated with MLA should be identified as target lesions and recorded and measured. Target lesions should be selected on the basis of their size (lesions with the longest diameter), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly should be selected. When there are too many measurable lesions, choose the largest three lesions as target lesions to follow. The other measurable lesions should be considered evaluable for the purpose of objective status determination.

Non-target lesions: All non-measurable lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks before the beginning of the treatment.

Clinical lesions: Clinical lesions will only be considered measurable on brain MRI when they are ≥ 5 mm diameter as assessed using a ruler.

Histology: This technique can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases when biopsy or surgical resection of a measureable lesion is clinically indicated.

Perfusion/CBV: This advanced brain MRI technique can be used as an adjunct test to determine treatment response or disease status. However, it should not be used as the primary or sole method to determine response or disease status.

Brain FDG-PET coupled with head CT or brain MRI: This advanced metabolic imaging technique can be used as an adjunct test to determine response or disease status. However it should be used as the primary or sole method of determining response or disease status.

11.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all target lesions sustained for at least 4 weeks.

Progressive Disease (PD): At least a 25% increase in the sum of products of perpendicular diameters of at least 1 target lesion, taking as reference the smallest sum of products of perpendicular diameters on study (this includes the baseline sum if that is the smallest on study). The absolute increase in any dimension must be at least 5mm when calculating the products of perpendicular diameters.

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

11.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Summary of the RANO Response Criteria (Adapted from JCO 2010)

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

Abbreviations: RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.
* Progression occurs when this criterion is present.
† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

11.3.4 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.3.5 Neurological Exam and Performance Status

Patients will be graded using the Karnofsky Performance Status scale and their neurological function evaluated as improved, stable or deteriorated in addition to objective measurement of tumor size. These parameters will be used to determine the overall response assessment.

11.3.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QASMC audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator

becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

13.0 STATISTICAL CONSIDERATIONS

This study will include 40 patients with high grade glioma (WHO grades III or IV). Based on an extensive simulation regarding the sample size for translational and pilot studies, Piantadosi (2005) recommended that a sample size of 10 to 20 patients would provide a reasonable precision for estimating preliminary information. We therefore expect that the proposed sample size for this study will be adequate in estimating both safety and preliminary efficacy data.

13.1 Endpoints

13.1.1 Primary Endpoint

The feasibility of patient compliance to chronotherapy in HGG patients treated with TMZ will be the primary endpoint. Feasibility is defined as at least 80% overall compliance (8 of 10 patients) with assigned administration time. Compliance is defined as no more than one of five doses of temozolomide per cycle taken outside of the assigned administration time.

13.1.2 Secondary Endpoints

1. Number of patients experiencing lymphopenia, thrombocytopenia, neutropenia and anemia in each group as measured by standard blood draws. Thresholds for each event are listed in the table under Study Assessments below.

2. Score on FACT-BR quality of life survey between morning and evening treatment to quantitatively measure quality of life.

3. Progression-free survival as determined by chart review or patient visit.

4. Overall survival as determined by chart review or patient visit.

5. Correlation between sleep pattern and response to treatment in morning and evening groups.

13.2 Data Analysis

13.2.1 General Considerations

All data will be evaluated as observed, and no imputation method for missing values will be used. All data will be presented in a descriptive manner. Each cohort will be analyzed separately, and no multiplicity adjustment across cohorts will be

performed. All other analyses are considered as exploratory, even if statistical tests are used.

Descriptive statistics will be used to summarize the trial results, i.e., statistics for continuous variables may include means, medians, ranges and appropriate measures of variability. Qualitative variables will be summarized by counts and percentages. The uncertainty of estimates will be assessed by confidence intervals. Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Counts of missing observations will be included in the denominator and presented as a separate category if not otherwise specified in the statistical analysis plan (SAP).

Duration of response, according to RANO, will be calculated for each subject and will be analyzed using the Kaplan-Meier method in the primary cohorts separately.

PFS will be presented in subject listings and analyzed using the Kaplan-Meier method in the primary cohorts separately.

Correlation analysis (significance at $R^2 \geq 0.8$) and slope analysis (Fisher's Exact Test) of dependent variables (naps/day, nap duration, sleep duration, % activity during waking, % activity during sleep, chronotype, chronotype variability) and independent variables (tumor grade, time since TMZ administration, time of day of TMZ administration, time since diagnosis date, tumor size, immune health) will be carried out. Each variable will be calculated daily and averaged over the collection period. Daily calculation reveals stability, while the average reveals variability.

13.2.2 Safety

13.2.2.1 Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs).

AEs will be classified using MedDRA with descriptions by System Organ Class and Preferred Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the study drugs will be categorized as related or unrelated.

Summary tables will be presented to show the number of subjects reporting TEAEs by severity grade and corresponding percentages. A subject who

reports multiple TEAEs within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. AE descriptions will be presented in order of decreasing frequency for System Organ Class, and by decreasing frequency in the overall or total column for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of AEs:

- Study-drug-related AEs
- AEs that are Grade ≥3, 4, or 5 in severity
- AEs leading to study drug interruption and/or dose modification
- AEs leading to study drug discontinuation
- SAEs (with categorization of the primary reason that the AE is considered serious, eg, life-threatening, hospitalization)

13.2.2.2 Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by ≥1 grade in the period from the first study drug administration to 30 days after the last study drug administration. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥1 in severity) will be considered treatment-emergent.

Test data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the laboratory will be used to determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Test data will be summarized in tables and may be summarized in figures showing values over time, if informative. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (eg, during the study or during a cycle).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to each time point. For parameters for which a CTCAE scale does not exist, shift tables

will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each time point (normal, low and high [or abnormal]). For selected variables of interest, tables may be prepared to show frequencies adjusted for baseline values; for these frequencies, subjects with the same or worse grade at baseline are not considered.

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Appendix A: Karnofsky Performance Status Scale

Definition	Score	Criteria
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 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.

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Appendix B: FACT-BR Quality of Life Survey

Below is a list of statements that other people with your illness have said are important**.** **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very muc**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7</u> <u>days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

Appendix C: Quality of Sleep Questionnaire

1. What time do you typically go to bed on weekdays? ___:___ am/pm

2. How long does it take you to fall asleep? _____(hours/min)

3. What time do you typically wake up on weekdays? ___:___ am/pm
    a. Do you use an alarm clock/wake up call? YES NO
    b. Do you feel refreshed upon waking up? YES NO

4. What time do you typically go to bed on the weekend/days off? ___:___ am/pm

5. How long does it take you to fall asleep? _____(hours/min)

6. What time do you wake up on the weekend/days off? ___:___ am/pm
    a. Do you use an alarm clock/wake up call? YES NO
    b. Do you feel refreshed upon waking up? YES NO

7. How many times do you wake up on a typical night? _____

8. Do you have difficulty falling back to sleep? YES NO

9. Check typical causes for awakening at night:
    a. Snoring
    b. Pain
    c. Full bladder
    d. Noise
    e. Nightmares
    f. Worry
    g. Thirst/hunger
    h. Bed partner/kids/pets
    i. Night sweats
    j. Headache
    k. Heartburn
    l. Choking/gasping

Please list other causes: _____

10. Do you nap intentionally? YES NO
    a. If yes, how many days per week? _____
    b. What time of day? _____
    c. How long are naps? _____
    d. Do you feel refreshed upon waking up from the nap? YES NO

11. Do you have problems getting to sleep or staying asleep? YES NO

12. Please rate the current, (i.e. the last 2 weeks) SEVERITY of your insomnia problem(s):

	None	Mild	Moderate	Severe	Very
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problem waking up too early	0	1	2	3	4

	Very Satisfied				Very Dissatisfied
1. How SATISFIED or DISSATISFIED are you with your current sleeping pattern?	0	1	2	3	4
	Not at all Interfering	**A Little**	**Somewhat**	**Much**	**Very Much Interfering**
2. To what extent do you consider your sleep problem to INTERFERE with your daily functioning? (i.e., daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)	0	1	2	3	4
	Not at all Noticeable	**Barely**	**Somewhat**	**Much**	**Very Noticeable**
3. How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?	0	1	2	3	4
	Not at all	**A Little**	**Somewhat**	**Much**	**Very Much**
4. How WORRIED or DISTRESSED are you about your current sleep problem?	0	1	2	3	4