Phase II Trial of VELCADE® (Bortezomib) in Combination with Temozolomide and Regional Radiation Therapy for Upfront Treatment of Patients with Newly-diagnosed Glioblastoma Multiforme.

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University of California at Los Angeles

STUDY PROTOCOL

Protocol Number X05303

[redacted]

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Investigator &Study Center:

Principal Investigator

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Co-Principal Investigator

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Sub-Investigators

[redacted]

Sub-Site:

[redacted]

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PROTOCOL SUMMARY

Title:

Phase II Trial of VELCADE* (Bortezomib) in Combination with Temozolomide and Regional Radiation Therapy for Upfront Treatment of Patients with Newly-diagnosed Glioblastoma Multiforme.

Objectives:

This phase II study will examine the safety and efficacy of bortezomib in combination with temozolomide/radiation followed by bortezomib and temozolomide for 2 years (24 28-day cycles) in newly-diagnosed patients with glioblastoma.

The primary objective of the study is to:

- Estimate the overall survival in subjects with newly-diagnosed glioblastoma (GBM) treated with bortezomib/temozolomide/radiation followed by bortezomib/temozolomide for 24 cycles until progression is detected or for up to 24 cycles (~2 years).

The secondary objectives of this study are to:

- Investigate further the safety and tolerability of bortezomib/temozolomide/radiation followed by bortezomib/temozolomide.
- Collect frozen and paraffin patient tumor tissue to be utilized for MGMT promoter methylation and IDH1 genotyping and for correlative molecular characterization to be submitted as a separate research study. Tissue must be obtained in all study patients from original surgery, and in those patients who will be undergoing resection at time of treatment failure and during the follow-up period.

Patient population:

This study will be open to newly-diagnosed patients with GBM that have not received other therapy other than surgery. Additionally, a key enrollment inclusion criterion is the collection of frozen tissue along with paraffinized tissue. This is necessary for MGMT promoter methylation and IDH1 genotyping studies and correlative molecular characterization. Specific inclusion and exclusion criteria are detailed in section 3.2.

Number of patients:

Total: 50 (over three year enrollment period)

Study design and methodology:

This will be a multi-center, open-label, phase II study assessing safety and efficacy in which adult newly-diagnosed GBM patients that have had no prior therapy, other than surgery, will receive bortezomib, temozolomide, and radiation all starting on day 1 (+/- 2 days) of study. Day 1 of the study must be no sooner than 2 weeks from surgery and no longer than 6 weeks after surgery, followed by bortezomib and temozolomide after completion of fractionated radiation for up to 24 additional cycles if no tumor growth is seen. At this point, both bortezomib and temozolomide will be discontinued, and the patient will be monitored with routine MRI surveillance until progression. There has recently been publication of a phase I study that found no significant toxicities when bortezomib at a dose of 1.3 mg/ m^2 (days 1, 4, 8, 11, 22, 25, 29, and 32) was combined with brain radiation and temozolomide for patients with newly-diagnosed or recurrent gliomas (Kubicek, Werner-Wasik et al. 2008). Of note, in the recurrent cases, patients had received prior radiation. Based on those findings, we will utilize the same bortezomib dosing used in that protocol, although the schedule will be slightly altered.

Patients will receive 1.3 mg/m^2 bortezomib subcutaneous on days 1, 4, 8, 11, 29, 32, 36, and 39 and temozolomide 75 mg/m^2 daily during radiation. Bortezomib will be administered beginning on the first day of radiation with temozolomide. External beam fractionated regional radiation will be given on consecutive week days at 200 cGy daily doses to a total dose of 6000 cGy. After a 2-6 week rest (for temozolomide and bortezomib) following completion of radiation therapy, a maintenance phase (post-RT) of temozolomide will be restarted at 150 mg/ m^2/day for 5 days out of every 28. (If this is tolerated, subsequent cycles will be given at 200 mg/ m^2/day). Also, bortezomib at 1.3 mg/m² will be given on days 1, 4, 8, and 11 of a 28 day cycle commencing on the first day of temozolomide. Temozolomide will not be increased greater than 200 mg/m^2/day. No increases in bortezomib above 1.3 mg/m² will be made. Treatment with bortezomib and temozolomide will continue for 24 additional 28 day cycles from radiation therapy if there is no evidence of progression. At that time, both bortezomib and temozolomide will be stopped if there is no evidence of disease progression. Note: If unacceptable toxicities after the first 12 cycles are observed, per investigator's discretion, the bortezomib dosing schedule may be changed to 1.3 mg/m^2 weekly for 3 weeks on and 1 week off, with the possibility of further reduction if necessary to 1.3 mg/m^2 biweekly.

Treatments administered:

1) Radiotherapy
2) Temozolomide
3) Bortezomib

Efficacy data collected:

The following evaluations will be conducted to assess the efficacy of the combination of bortezomib, temozolomide and radiation:

- Overall survival
- Time to progression
- Progression free survival
- Radiographic response (when evaluable)

Pharmacokinetic/Pharmacodynamic/Pharmacogenomic/Correlative studies:

[redacted]

Safety data collected:
The following evaluations will be conducted to assess the safety of VELCADE:

- **Toxicity/safety:** Patients will be assessed using CTC 3.0.

Statistical procedures:

The sample size calculation for this one-arm trial is based on an endpoint of an 18-month survival rate with a 36-month accrual period (1-2 patients/month). The following assumptions are made: 1. Survival time follows an exponential distribution, 2. The 18-

month survival rate is 55% (median survival 21 months) for the new treatment and 40% (median survival 14 months) for the standard treatment (based on (Stupp, Mason et al. 2005), 3. The 18-month survival rate is estimated using the Kaplan-Meier method, 4. Test statistics – Z-test, Type I error=0.05, 5. N=50 (total patients). In a performed simulation, the power is 70% for 1-sided test.

After 10 patients with newly-diagnosed GBM are treated, an interim analysis will be conducted. If 3 or more patients have experienced unacceptable toxicity (defined as a grade 4 non-hematologic toxicity or any grade 5 toxicity), enrollment will be suspended pending full assessment of safety risks to determine if the study should continue. Otherwise, patient accrual will continue.

The primary endpoint will be total survival from the date of surgical-pathological diagnosis. For the final analysis, endpoint results will be compared with the results on comparable patients whose data are available through the UCLA Neuro-Oncology Department database. These comparable patients were all newly diagnosed GBM patients who were treated on research protocols and similar to the patients in the present study insofar as were seen at a tertiary center and enrolled into clinical trials early after diagnosis. The primary analysis will utilize a Cox proportional hazards model including age, KPS, and extent of resection. This allows for adjustment for major prognostic factors.

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Abbreviations List

Abbreviation	Definition
°C	degrees Celsius
μM	Micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
CAM	cell adhesion molecules
Cm	Centimeter
CR	Complete Response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
dL	Deciliter
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
GBM	Glioblastoma
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Ht	Height
IκB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
IκBα	I kappa B alpha-associated protein kinase
Kg	Kilogram
Ki	inhibitory constant
Lbs	Pounds
m^2	square meters
Mg	Milligram
Min	Minute
mL	Milliliter

Abbreviation	Definition
mm^3	cubic millimeters
Mmol	Millimole
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NF-κB	nuclear factor-κB
Ng	Nanogram
nM	Nanomole
p21	p21(ras) farnesyl-protein transferase
p27	cyclin-dependent kinase inhibitor
p53	tumor suppressor protein with molecular weight of 53 kDa
PR	Partial response
RT	Radiation therapy
SAE	serious adverse event
SQ	subcutaneous
TMZ	temozolomide
UCLA	University of California at Los Angeles
US	United States
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
Wt	Weight

1 INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

The incidence of primary malignant brain tumors in the United States (US) is about 17,000 per year, with approximately 10,000 deaths per year (Wrensch, Minn et al. 2002). Glioblastoma is the most frequent, accounting for ~40% of all primary malignant brain tumors. It is the most aggressive form of brain cancer. Although they are relatively uncommon, malignant brain tumors account for significant mortality in the US. Despite optimal treatment with surgery, radiation therapy, and chemotherapy, the prognosis remains poor. Recently, a phase III randomized trial comparing radiation alone with combined temozolomide and radiation followed by 6 cycles of temozolomide showed that the addition of temozolomide increased median survival from 12.1 months to 14.6 months, increasing 2-year survival rates from 10.4% to 26.5% (Stupp, Mason et al. 2005). These results have established adjuvant temozolomide and radiation as the standard of care for newly-diagnosed glioblastoma. Nonetheless, there is clearly a need for improvement given that this regimen is associated with a two-year survival of only 26%. The proposed trial will evaluate whether the addition of bortezomib to radiation and temozolomide can be safely tolerated, and whether this combination has increased efficacy in the treatment of newly-diagnosed glioblastoma. The major safety issues that are anticipated to require close monitoring are myelotoxicity (particularly thrombocytopenia), and any unpredicted neurological side effects secondary to bortezomib and brain radiation.

Accumulating evidence indicates that NF-kB may be constitutively active in glioblastoma (Raychaudhuri, Han et al. 2007). NF-kB may potentially have a key role in tumor processes such as invasion, suppression of apoptosis, angiogenesis, proliferation, and chemotherapeutic and radiation resistance. Thus, targeting NF-kB activation has emerged as an anti-tumor strategy. Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell.

Bortezomib has gained United States Food and Drug Administration (US FDA) approval for myeloma in the relapsed and frontline setting, and in relapsed mantle cell lymphoma. Its primary mechanism of action is thought to be mediated by repression of NF-kB signaling by stabilization of IkB (Orlowski and Kuhn 2008). There is preclinical evidence demonstrating activity of bortezomib against glioblastoma (Yin, Zhou et al. 2005; Styczynski, Olszewska-Slonina et al. 2006). Bortezomib causes growth arrest of human GBM cell lines and GBM explants via NF-kB inhibition that can be enhanced by TNF alpha or TNF-related apoptosis-inducing ligand (TRAIL) (Yin, Zhou et al. 2005). The clinical trial experience in actual patients has not been published, and is limited to recurrent patients (tamoxifen/bortezomib (Cedars-Sinai), temozolomide/bortezomib (City of Hope), and bevacizumab/bortezomib (Duke)) Bortezomib and Concurrent External Beam Radiation (Universty of Colorado), Bortezomib with Concurrent Fixed Dose Paclitaxel and Radiation (University of Colorado), Concomitant Bortezomiband Radiation (NCI), Bortezomib as a Radiosensitizer in Patients with Metastatic Melanoma to the Brain who Require Whole Brain Radiation (University of Michigan), Bortezomib, Paclitaxel, Carboplatin, and Concurrent Thoracic Radiation Therapy (NCCTG). In other tumor types, there is evidence of enhancement of either temozolomide or radiotherapy with concurrent administration of bortezomib (Russo, Tepper et al. 2001; Amiri,

Horton et al. 2004; Edelman 2005). For example, melanoma cells *in vitro* and in the context of murine models were significantly more sensitive when treated with the combination of bortezomib and temozolomide compared to temozolomide alone (Amiri, Horton et al. 2004). Increased levels of NF-kB activity has been implicated in tumor resistance to temozolomide (Bredel, Bredel et al. 2006; Yamini, Yu et al. 2007).

Recently, bortezomib with concurrent radiotherapy and temozolomide has been studied in a phase I trial for central nervous system malignancies, including newly-diagnosed and recurrent malignant gliomas (Kubicek, Werner-Wasik et al. 2008). Only temozolomide was continued after radiation for maintenance. At the highest dose used (1.3 mg/m^2, days 1, 4, 8 and 11 of a 21 day cycle given twice), no dose-limiting toxicities were reported. The most frequent toxicities were Grade 1 and 2 stomatitis, erythema, and alopecia. Grade 3 toxicities reported were headache, neuropathy, syncope, hyponatremia, and dyspnea. This study adds to the currently limited experience treating humans with concurrent bortezomib and radiation.

In preclinical models, bortezomib is a radiosensitizer (Davies, Lara et al. 2007). There are ongoing studies utilizing the combination of bortezomib and radiation therapy (RT) for a variety of solid tumors. In a study utilizing bortezomib (0.6 mg/ m² twice weekly) and re-irradiation for recurrent head-and-neck squamous cell carcinoma (HNSCC), there was no clear relationship between the bortezomib/RT combination and observed DLTs (Van Waes, Chang et al. 2005). Particularly, no excessive mucositis was observed. In case reports in which multiple myeloma was treated with concurrent RT and bortezomib, apparent increased local GI toxicity was observed (Berges, Decaudin et al. 2008).

In summary, the rationale for the study is based on: 1) current inadequacy of standard of care therapy for newly-diagnosed glioblastoma, 2) preclinical evidence indicating activity of bortezomib against glioblastoma and possible synergism with temozolomide and/or radiation, and 3) demonstrated feasibility of such a similar study conducted at UCLA and the possibility of more rapid enrollment and 4) tissue collection (serum and tumor tissue) and banking for correlative studies aimed at understanding biomarkers and mechanisms of tumor response to bortezomib within this context.

1.2 VELCADE (bortezomib) for Injection

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.3 Temozolomide (see product insert)

1.3.1 Scientific Background

Temozolomide is an oral DNA alkylating agent that is FDA approved for the treatment of malignant gliomas. It is a derivative of dacarbazine and is rapidly converted systemically to MTIC. It interferes with DNA replication via alkylation of specific sites of the nucleotide backbone. Perhaps the most important site is on the O6 position of guanine. Alkylation of this site can be repaired by the enzyme, O-6-methylguanine-DNA methyltransferase (MGMT). Promoter methylation of MGMT has emerged as a marker of response to temozolomide.

1.3.2 Nonclinical Pharmacology

Not applicable

1.3.3 Nonclinical Toxicity

Not applicable

1.3.4 Clinical Pharmacokinetics and Pharmacodynamics

See product insert. http://www.spfiles.com/pitemodar.pdf

1.3.5 Clinical Experience

See product insert. http://www.spfiles.com/pitemodar.pdf

1.3.6 Potential Risks of Temozolomide

See product insert. http://www.spfiles.com/pitemodar.pdf

1.4 Study rationale and selection of drug doses

The present proposal seeks to investigate whether beneficial effects can be detected when bortezomib is combined with first-line treatment with temozolomide/XRT in patients with newly-diagnosed glioblastoma.

Accumulating evidence indicates that NF-kB may be constitutively active in glioblastoma (Raychaudhuri, Han et al. 2007). Given the potential for NF-kB to have a key role in tumor processes such as invasion, suppression of apoptosis, angiogenesis, proliferation, and chemotherapeutic and radiation resistance, targeting NF-kB activation has emerged as an anti-tumor strategy. Bortezomib is a proteasomal inhibitor that has gained FDA approval for both myeloma and relapsed mantle cell lymphoma. Its primary mechanism of action is thought to be mediated by repression of NF-kB signaling by stabilization of IkB (Orlowski and Kuhn 2008). There is preclinical evidence of activity of bortezomib against glioblastoma (Yin, Zhou et al. 2005; Styczynski, Olszewska-Slonina et al. 2006). Bortezomib causes growth arrest of human GBM cell lines and GBM explants via NF-kB

inhibition, and could be enhanced by TNF alpha or TNF-related apoptosis-inducing ligand (TRAIL) (Yin, Zhou et al. 2005). The clinical trial experience in actual patients has not been published and is limited to recurrent patients (tamoxifen/bortezomib (Cedars-Sinai), temozolomide/bortezomib (City of Hope), bevacizumab/bortezomib (Duke). In other tumor types, there is evidence of enhancement of either temozolomide or radiotherapy with concurrent administration of bortezomib (Russo, Tepper et al. 2001; Amiri, Horton et al. 2004; Edelman 2005). Increased levels of NF-kB activity has been implicated in tumor resistance to temozolomide (Bredel, Bredel et al. 2006; Yamini, Yu et al. 2007).

Recently, bortezomib with concurrent radiotherapy and temozolomide has been studied in a phase I trial for central nervous system malignancies, including newly-diagnosed and recurrent malignant gliomas (Kubicek, Werner-Wasik et al. 2008). Only temozolomide was continued after radiation for maintenance. At the highest dose used (1.3 mg/m^2, days 1, 4, 8 and 11 of a 21 day cycle given twice), no dose-limiting toxicities were reported for bortezomib. The most frequent toxicities were Grade 1 and 2 stomatitis, erythema, and alopecia. Grade 3 toxicities reported were headache, neuropathy, syncope, hyponatremia, and dyspnea. This study adds to currently limited experience treating humans with concurrent bortezomib and radiation. In preclinical models, bortezomib is a radiosensitizer (Davies, Lara et al. 2007). There are ongoing studies utilizing the combination of bortezomib and RT for a variety of solid tumors. In a study utilizing bortezomib (0.6 mg/ m^2 twice weekly) and re-irradiation for recurrent head-and-neck squamous cell carcinoma (HNSCC), there was no clear relationship between the bortezomib/RT combination and observed DLTs (Van Waes, Chang et al. 2005). Particularly, no excessive mucositis was observed. In case reports in which multiple myeloma was treated with concurrent RT and bortezomib, apparent increased local GI toxicity was observed (Berges, Decaudin et al. 2008).

Another feature of this trial is the requirement for frozen and paraffinized patient tumor tissue for molecular characterization. We have recently completed enrollment of a similar trial in which frozen tumor tissue was required (Lai, Filka et al. 2008). This is a 70-patient trial examining the safety and efficacy of upfront bevacizumab, temozolomide, and radiaton for the treatment of newly-diagnosed glioblastoma. The detailed tissue interrogation for the bevacizumab/TMZ/RT has not yet begun, although fairly detailed plans have been formulated. Planned assays for the bevacizumab/TMZ/RT study include MGMT promoter methylation and immunohistochemistry VEGF and VEGFR immunohistochemistry gene expression, SNP (for copy number), and methylation microarray based profiling. We anticipate that much of the experience and information gained from characterizing this tissue will be directly applicable to the proposed patient sample set.

In summary, the rationale for the study is based on: 1) current inadequacy of standard of care therapy for newly-diagnosed glioblastoma, 2) preclinical evidence indicating activity of bortezomib against glioblastoma and possible synergism with temozolomide and radiation, and 3) demonstrated feasibility of such a similar study conducted at UCLA and the possibility of more rapid enrollment and tissue interrogation leading to understanding of biomarkers and mechanisms of tumor response to bortezomib within this context.

The selection of RT and TMZ dosing is based entirely on the Stupp protocol for newly-diagnosed GBM (Stupp, Mason et al. 2005). Based on the recent phase I study, patients will receive 1.3 mg/ m^2/day on days 1, 4, 8, 11, 29, 32, 36, and 39 during radiation (Kubicek, Werner-Wasik et al. 2008). The 1.3 mg/ m^2/day dose (days 1, 4, 8, and 11 of a 28 day cycle) will be the maintenance dose for all patients. This is the dose previously used in combination

with TMZ maintenance therapy without evidence of significant toxicity (personal communication, Dr. Portnow, City of Hope, Duarte, CA).

2 STUDY OBJECTIVES

This phase II study will have a **Radiation phase** with bortezomib in combination with temozolomide/radiation followed by a **Maintenance phase** of bortezomib and temozolomide following completion of radiation for 2 years (24 28-day cycles).

2.1 Primary Objective

The primary objective of this study is to:

- Estimate the overall survival

  Investigate the safety and tolerability of this drug combination (bortezomib with temozolomide/radiation followed by bortezomib and temozolomide maintenance for 2 years if there is no progression, in which case both drugs will be stopped, and the patient will obtain routine MRI surveillance until progression) in newly-diagnosed patients with glioblastoma.

2.2 Secondary Objectives

The secondary objectives of this study are to**:**

- Investigate further the safety and tolerability of bortezomib/temozolomide/radiation followed by bortezomib/temozolomide.
- Collect frozen and paraffinized patient tumor tissue for MGMT promoter methylation analysis and IDH1 genotyping and for correlative studies. Tissue must be obtained in all study patients from the original surgery, and in those patients who will be undergoing resection at time of treatment failure and during the follow-up period.

3 INVESTIGATIONAL PLAN

3.1 Overall Design and Plan of the Study

This study will be a multi-center, open-label, phase II study assessing safety and efficacy in which adult newly-diagnosed GBM patients that have had no prior therapy other than surgery will receive bortezomib, temozolomide, and radiation all starting on day 1 (+/- 2 days) of study. Day 1 of the study must be no sooner than 2 weeks from surgery and no longer than 6 weeks after surgery, followed by bortezomib and temozolomide after completion of fractionated radiation for up to 24 additional cycles if no tumor growth is seen. At this point, both bortezomib and temozolomide will be discontinued and patients will be monitored with routine MRI surveillance till progression.

Patients will be treated with bortezomib 1.3 mg/ m² SQ on days 1, 4, 8, 11, 29, 32, 36, and 39 and temozolomide 75 mg/m^2 daily during radiation. Bortezomib will be administered beginning on the first day of radiation with temozolomide. External beam fractionated regional radiation will be given on consecutive week days at 200 cGy daily doses to a total dose of 6000 cGy (see Appendix 8.12). Although the preferred two week rest period contrasts with the 4 week rest period used in the phase III radiation/temozolomide trial (Stupp, Mason et al. 2005), we will attempt to shorten the rest period to 2 weeks in order to minimize treatment delay. This shortened rest period has been safely used in a study examining the effect of upfront temozolomide and cis-retinoic acid and radiation (Butowski, Prados et al. 2005). The 2-week rest period is also consistent with our current clinical practice. However, if the patient has fatigue, bone marrow suppression, or other toxicities, the temozolomide rest period may be extended up to six weeks. After a 2-6 week rest (for temozolomide and bortezomib) following completion of radiation therapy, temozolomide will be restarted at 150 mg/ m²/day day 1-5 of every 28 day cycle. If this dose is tolerated, subsequent cycles will be given at 200 mg/ m²/day. Bortezomib will be given at a dose of 1.3 mg/m²on days 1, 4, 8, and 11 of a 28 day cycle commencing on the first day of temozolomide. Temozolomide will not be increased greater than 200 mg/ m²/day. No increases in bortezomib will be allowed. Treatment with bortezomib and temozolomide will continue for 24 additional 28 day cycles following completion of radiation therapy if there is no evidence of progression. At that time, both bortezomib and temozolomide will be stopped if there is no evidence of disease progression. If unacceptable toxicities after the first 12 cycles are observed per investigator's discretion, the bortezomib dosing schedule may be changed to 1.3 mg/m^2 weekly for 3 weeks on and 1 week off, with the possibility of further reduction if necessary to 1.3 mg/m^{2}biweekly. Overall survival, 6-month progression free survival, and time to progression will be reported. An interim analysis will be conducted on the first 10 patients. This patient cohort will be monitored for unanticipated or unacceptable toxicities related to the combination of bortezomib and brain radiation, as well as focusing on delayed effects of radiation 4 weeks after the completion of radiation therapy. Specifically, we will be looking for increased rates of brain hemorrhage, necrosis, and scalp wound healing problems. Common adverse events such as myelosuppression or deep venous thrombosis (occurring in ~30% of patients with high-grade glioma (Robins, Won et al. 2006)) will also be carefully reviewed to determine whether they are related to the bortezomib combination. Unless a clear causal relationship is demonstrated, such adverse advents will not be considered a toxicity due to bortezomib/RT combination therapy.

CLINICAL AND LABORATORY EVALUATIONS

Pre-treatment Evaluations

-A complete history and physical (to include height, weight, and BSA), vital signs (including blood pressure) and neurological examination (to include mental status, neurological function, and documentation of the patients Karnofsky performance status), as well as neuro-imaging documentation of disease shall be performed on all patients within 21 days prior to initiation of treatment. In patients that have had immediate post-operative MRI scans, this will likely necessitate a repeat baseline MRI scan if treatment is initiated much greater than 21 days after resection.

-Pre-study laboratory tests must include CBC with differential and platelets, serum creatinine, BUN, total bilirubin, SGOT, SGPT, serum electrolytes (including Na, Cl and K),PT, PTT, INR, glucose, albumin, alkaline phosphatase, calcium, total protein, urine test and creatinine clearance (calculated), anti-convulsant levels if applicable, and a serum pregnancy test for women of childbearing potential. Pre-study laboratory tests must be obtained within 14 days of initiation of treatment. Any abnormal pre-study laboratory tests must be rechecked within 48 hours of initiating therapy.

- Documentation of tumor diagnosis. Following registration, slides from the pre-registration biopsy must be submitted to UCLA for review.

- Unstained paraffin block or slides from surgical samples: A paraffinized tumor block must be obtained in all study patients from the surgery in which frozen tissue was collected, and in those patients who will be undergoing resection at time of treatment failure and during the follow-up period. If such a tumor block cannot be obtained then 1 H & E stained slide and 20 unstained paraffin slides may be submitted instead. Collection of an unstained paraffin block is optional in the follow-up part of the trial. The paraffin block/slides will be used for MGMT methylation analysis and IDH1 genotyping.

-Frozen surgical samples: A frozen tumor block sample will be obtained in all study patients at the time of surgery, and in those patients who will be undergoing resection at time of treatment failure and during the follow-up period. Collection of frozen tissue is optional in the follow-up part of the trial. Frozen tissue will be used to verify MGMT methylation and IDH1 genotyping and for correlative studies.

[redacted]

[redacted]

Evaluations During Treatment

A. Evaluations to be obtained prior to and during the concomitant therapy with bortezomib, temozolomide and radiation:

- Laboratory studies: CBC with differential and platelets will be performed weekly during radiation treatment. Creatinine, BUN, total bilirubin, SGOT, glucose, albumin, alkaline phosphatase, SGPT, calcium, total protein, serum electrolytes (including Na, Cl and K) will be performed every 2 weeks during radiation.

- Plasma and serum collection prior to each treatment cycle on day 1 of each 28 days treatment cycle.

- Whole blood sample at initiation of treatment.

[redacted]

Plasma Sample Collection and Preparation:

Collect 5 mL of whole blood into a CTAD (B-D Cat #367947 Hemogard, 4.5 mL tube) blue top vacutainer tube, being careful to minimize agitation of the sample and using the largest-bore needle that is feasible for the patient. Mix by gently inverting the tube 4 times. Centrifuge at 2000 x g for 15 minutes at room temperature within 1 hour of draw. Within 30 minutes after centrifugation, draw off plasma very slowly with transfer pipette to within 0.5 cm of the buffy coat, taking great care not to disturb the buffy coat. (Any contamination may invalidate the assay.) Pipette the plasma specimen equally into plastic cryovials. Do not transfer more than 1.5 mL into each tube. Label tube with subject identification number, initials, and date of specimen collection. [redacted]

Serum Sample Collection and Preparation:

Collect 5 mL of blood in one red top tube. Immediately mix by inverting tubes 4 times. Complete the pre-printed labels with subject identification numbers, initials, and date of specimen collection. Allow serum to clot for 30 minutes. Spin at 2000 x g for 15 minutes to separate clot from serum. Pipette no more than 1.5 mL of serum specimen into plastic cryovials. All specimens must be stored frozen at -20° C (or colder) until pickup.

Whole Blood Sample Collection and Preparation:
Collect 8.5 mL blood in one PAXgene Blood DNA tube.

1. Ensure that the PAXgene Blood DNA Tube is at room temperature (18-25°C)prior to use and properly labeled with patient identification.

2. The PAXgene Blood DNA Tube should be the last tube drawn.

3. After blood collection, gently invert the PAXgene Blood DNA Tube 8 - 10 times.

4. Freeze PAXgene Blood DNA Tubes upright in a wire rack or horizontally in a plastic bag at -20° C (or colder).Do not freeze tubes upright in a Styrofoam® collection tray as this may cause the tubes tocrack.

- A neurologic exam must be performed every two weeks during radiation therapy, to include: the patient's Karnofsky performance status, neurological function, and mental status. A general physical exam must also be performed every two weeks during radiation, to include: examination of the skin within the treatment portal And evaluation for adverse events These adverse events will be documented in the medical record, on the Flow sheet CRF, and reported to the principal investigator. Adverse events in subsequent cycles will be reported prior to the beginning of each cycle. Height, weight, and BSA must be evaluated prior to each cycle.

- MRI of the brain with and without gadolinium contrast is required within 21 days of Day 1 of the study. A postoperative MRI scan within 96 hours of surgery is also preferred.

Evaluation during the radiation therapy:

Procedures	Prior to Treatment	Every week	Every 2 weeks	Every 4 weeks	At week 6
History, physical exam, height/weight	X [g]		X	X	X
Neurologic Evaluation	X [g]		X	X	X
Routine blood test	X[a]	X		X	X
Urine test	X				
Research blood test[f]	X[f]			X	
MRI head	X [h]				
Pregnancy test	X[b]				
Pathology slides/frozen tissue	X				
Study Treatment with Bortezomib[d]		X Days 1, 4, 8, 11, 29, 32, 36, 39			
Study Treatment with Temozolomide[c]		X Days 1 - 42			
Radiation therapy[e]		X for 6 weeks			

[a] Must be obtained within 14 days prior to starting treatment (weekly during radiation therapy).
[b] for female patients of childbearing potential
[c]TemozolomideDay 1 –42 during radiation therapy.
[d]Bortezomibon day 1, day 4, day 8 , day 11, day 29, day 32, day 36 and day 39 during radiation therapy.
[e] Radiotherapy will be administered in 2Gy/day fractions delivered 5 days per week to a total dose of 60Gy over a six week period.
[f]Research blood test (on day 1 of a 28 day treatment cycle.)
[g] Must be obtained within 14 days prior to treatment and every 2 weeks during radiation therapy
[h] Must be obtained within 21 days of Day 1 of the study.

B. Evaluations to be obtained after completion of radiation, during maintenance phase with bortezomib and temozolomide:

- In general, a cycle is defined as a four-week interval starting from the first bortezomib/temozolomide dose given post-radiation. If temozolomide is started first (if, for example, bortezomib is delayed because of peripheral neuropathy), wait to begin bortezomib until day 1 of the next four-week cycle. Always begin bortezomib on day 1 of a cycle, never mid-cycle.

- CBC with differential and platelets, creatinine, BUN, total bilirubin, SGOT, glucose, albumin, alkaline phosphatase, SGPT, calcium, total protein, and serum electrolytes (including Na, Cl and K) must be performed on days 21 and 28 (+/- 3 days). If cycle is held for any reason, labs must be repeated again before cycle initiation if labs greater than 3 days from Day 1.

- A neurologic exam must be performed every two weeks during radiation therapy and then every four weeks after radiation is completed (prior to the start of each new cycle). The exam must include: patient's Karnofsky performance status, neurological function, and mental status. A general physical exam must also be performed every four weeks after radiation is completed, to include: height, weight, BSA, and evaluation for any adverse events. Adverse events will be reported prior to the beginning of each cycle.

- MRI of the brain with and without gadolinium contrast is required within 21 days of Day 1 of the study. Then MRI will be performed 2 weeks ±7 days after completion of radiation, and then every 8 weeks ±7 days. CT scanning with and without contrast may be substituted if an MRI is medically contraindicated.

Evaluation to be Obtained During Bortezomib and Temozolomide after radiation

Studies	Day 1	Day 21	Day 29
History, physical exam, height/weight, toxicity	X		X
Neurologic Evaluation	X		X
Routine blood test	X	X	X
Research blood test [a]	X		X
MRI head [b]			
Temozolomide	X Days 1 – 5		X
Bortezomib	X Days 1, 4, 8, 11		X

[a]Research blood test on day 1 of a 28 day treatment cycle.
[b] MRI will be done 2 weeks after the end of the radiation therapy, then every 8 weeks.

- All relevant information regarding drug doses, concomitant medications and doses, measurable lesions, tumor response, laboratory examinations, and treatment-related toxicities shall be documented in the patient's medical record and case report form flow sheets.

- All patients will be followed for survival. Patients who progress will be followed for survival every 4 months. Patients who complete therapy and do not progress should be followed every 2 months for 12 months, every 3 months for the next 12 months, every 4 months for the next 12 months, and then every 6 months until progression is determined. They should then be followed for survival every 4 months. Patients will be asked to provide pathology slides and frozen tissue if they undergo elective surgery during the follow-up period. Collection of an unstained paraffin block and frozen tissue is optional in the follow-up part of the trial. Subjects will need to sign a separate consent form if they agree to donate the tissue samples.

- If patients remain on study drug for greater than one year, the study evaluations for neurologic exam and physical exam may be changed to every 8 weeks.

Central Review of MRI Scans

Post-Treatment Evaluations

Patients taken off study due to unacceptable toxicities or completion will be followed with a brain MRI at a minimum of every 2 months until progression is determined, and a neurological examination at a minimum of every 4 months.

A study flow chart is provided in section 0.

3.2 Selection of Patients

The total number of patients to be enrolled on this study is: 50. Enrollment is defined as the first day of VELCADE treatment (i.e., Day 1 of Cycle 1).

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

3.2.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Voluntary written informed consent obtained before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care. All

patients must sign an informed consent approved by the Institutional Review Board indicating that they are aware of the investigational nature of this study. Patients must also sign an authorization for the release of their protected health information.

- Female subject is post-menopausal for at least 1 year before the Screening visit, surgically sterilized, or if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time,(i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, condom with spermicide, or abstinence) from the time of signing the informed consent through 30 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse.
- Male subject even if surgically sterilized (ie, status postvasectomy), whoagrees to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study treatment, or agree to completely abstain from heterosexual intercourse.
- Patients will have a histologically proven intracranial glioblastoma multiforme (GBM) or gliosarcoma (GS). This includes treatment-naïve patients with prior tissue diagnoses of lower grade gliomas that have been upgraded to GBM after repeat resection.
- Cranial MRI or contrast CT must have been performed within 21days of study entry. The use of MRI rather than CT is preferred. The same type of scan, i.e., MRI or CT must be used throughout the period of protocol treatment for tumor measurement. If the surgical procedure was a resection, cranial MRI or contrast CT performed within 96 hours of resection is preferred, but not required. Patients without measurable or assessable disease are eligible.
- Patients must begin partial brain radiotherapy no sooner than 2 weeks and no later than 6 weeks from the surgery in which tissue was collected. Patients with GBM diagnosis from surgeries in which tissue was not collected will be eligible after repeat surgery is performed to collect tissue, as long as no treatment has been initiated prior to the surgery in which tissue was collected. In this case, initiation of treatment must begin within three to six weeks from the last surgery. Patients may have radiotherapy administered at outside facilities according to the specified guidelines (Appendix 8.12). Radiotherapy must be given by external beam to a partial brain field in daily fractions of 2.0 Gy, to a planned total dose to the tumor of 60.0 Gy in accordance with Appendix 8.12 Stereotactic radiosurgery and brachytherapy will not be allowed.
- Patients must be willing to forego other drug therapy against the tumor while being treated with bortezomib, temozolomide, and radiation, and subsequently bortezomib and temozolomide.
- Patients must be $\geq$ 18 years old, and with a life expectancy > 8 weeks.
- Patients must have a Karnofsky performance status of $\geq$ 60.
- Patients must have adequate bone marrow function (WBC $\geq$ 3,000/µl, ANC $\geq$ 1,500/mm^3, platelet count of $\geq$ 100,000/mm^3, and hemoglobin $\geq$ 10 gm/dl) and the test must be performed within 14 days prior to registration. Eligibility level for hemoglobin may be reached by transfusion.
- Patients must have adequate liver function (SGOT < 2.5 times ULN and bilirubin < 1.5 times ULN) and the test must be performed within 14 days prior to registration.
- Patients must have adequate renal function (creatinine < 1.5 mg/dL) before starting therapy and the test must be performed within 14 days prior to registration.

- Serum sodium >130 mmol/L

3.2.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

- Patient has a platelet count of $<100\times 10^9$/L within 14 days before enrollment.
- Patient has an absolute neutrophil count of $<1.5 \times 10^9$/L within 14 days before enrollment.
- Patient has a calculated or measured creatinine clearance of <20 mL/minute within 14 days before enrollment.
- Patient has ≥Grade 2 peripheral neuropathy within 14 days before enrollment.
- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see section 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.
- Patient has hypersensitivity to bortezomib, boron, or mannitol.
- Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women. Women with reproductive potential must practice adequate contraception for the duration of the study. The anti-proliferative effects of the investigational agent may be detrimental to the developing fetus or nursing infant.
- Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study including, but not limited to, ongoing or active infection requiring IV antibiotics, psychiatric illness/social situations that would limit compliance with study requirements, or disorders associated with a significant immunocompromised state (HIV, SLE, etc.);
- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy (such as cervical), or low-risk prostate cancer after curative therapy. Patients must be in complete remission and off of all therapy for that disease for a minimum of 3 years.
- Patients must not have received previous radiotherapy to the brain.
- Patients must not have received cytotoxic drug therapy, non-cytotoxic drug therapy, or experimental drug therapy directed against the brain tumor. Patients who received Gliadel wafers will be excluded. Patients may have received or be receiving corticosteroids, AED's, analgesics, and other drugs to treat symptoms or prevent complications.
- Since VELCADE is partially metabolized by inducers of CYP450 3A4 such as Enzyme-inducing anti-epileptic drugs (EIAED), patients on EIAED must be transitioned to non-EAIED at least 2 weeks prior to initiation of treatment.

- Patients must not have received previous radiotherapy to the brain.

General Medical Concerns

- Patients must not 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.
- Patients receiving current, ongoing treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin) are NOT excluded (see 1.2.2). However, since Velcade is weak inhibitor of CYP450 2C19, close monitoring of INR will be required.
- Patients must not have any disease that will obscure toxicity or dangerously alter drug metabolism.
- No viral hepatitis (hep B surface ag positive), or active hepatitis C infection.
- History of stroke within the past 6 months.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

VELCADE (bortezomib) for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing VELCADE and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of VELCADE contain 35 mg of mannitol.

Temozolomide (TEMODAR®) is commercially available, manufactured and distributed by Schering-Plough, Inc. The oral capsules contain a white to light tan/light pink powder. The molecule is stable at acidic pH (<5), and labile at pH >7, hence TEMODAR can be administered orally. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH. Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are white and imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake. *TEMODAR 20 mg:* brown imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide. *TEMODAR 100 mg:* blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD&C Blue #2 aluminum lake. *TEMODAR 250 mg:* black imprint contains pharmaceutical grade shellac, anhydrous ethylalcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

Radiation-see Appendix 8.11

3.3.2 Preparation, Handling, and Storage of Drugs

VELCADE (bortezomib)

Vials containing lyophilized VELCADE for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); excursions permitted from 15 to 30ºC (59 to 86ºF). For Europe, do not store above 30ºC (86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 3.5 mL of normal (0.9%) saline for intravenous or 1.4 mL for subcutaneous (see below), Sodium Chloride Injection USP, so that the reconstituted solution contains VELCADE at a concentration of 1 mg/mL. Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE should be administered promptly and in no case more than 8 hours after reconstitution. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Bortezomib Destruction

Investigational bortezomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Temozolomide

Tablets may be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). The commercial product has an expiration date on the label of the bottle.

Drug administration and dosage schedule

Administration and schedule of chemotherapy:

RT Phase: (Beginning 2-6 weeks post surgery)

Bortezomib1.3 mg/ m² SQ on days 1, 4, 8, 11, 29, 32, 36, and 39 during the 6 weeks of radiation.If dosing has to be delayed for any reason (such as holidays), subsequent treatments must be at least 3 days after prior dose.

Temozolomide75 mg/m2/day PO starting on Day 1 during radiation and continuing for 42 consecutive days.

External beam fractionated regional radiation will be given on consecutive week days at 200 cGy daily doses to a total dose of 6000 cGy.

Bortezomib	1.3mg/ m²	SQ	Days 1, 4, 8, 11, 29, 32, 36, 39 x 6 weeks
Temozolomide	75 mg/m2/day	PO	Day 1 x 42 consecutive days
XRT	200 cGy doses	XRT	Days Monday-Friday (total dose 6000 cGy)

Maintenance Phase: (Beginning after a 2-6 week rest post XRT)

Bortezomib 1.3 mg/ m² SQ will given on days 1, 4, 8, and 11 of a 28 day cycle commencing on the first day of temozolomide. Day 1dosing of any cycle can be delayed for any non-toxicity reason (such as holidays) for up to 7 days, with the subsequent cycle starting no earlier than 28 days from the beginning of the delayed cycle. Similarly, if day 4,8, or 11 treatments need to be delayed for any non-toxicity related reason, then subsequent treatments must be at least 3 days after delayed dose.

Temozolomide150 mg/m2/day day 1-5 of every 28 day cycle, increased to 200 mg/m^2/day beginning in the second post RT cycle if no toxicities observed.

Restaging with cranial MRI every 8 weeks, and continuing treatment for 24 additional 28 day cycles.

1st Cycle			
Bortezomib	1.3mg/ m²	SQ	Days 1, 4, 8, 11, of a 28 day cycle
Temozolomide	150 mg/m^2/day	PO	Day 1-5 of a 28 day cycle
2nd Cycle			
Bortezomib	1.3mg/ m^2	SQ	Days 1, 4, 8, 11, of a 28 day cycle for 24 additional cycles
Temozolomide	200 mg/m^2/day	PO	Day 1-5 of a 28 day cycle for 24 additional cycles

** Temozolomide will not be increased greater than 200 mg/m2/day. No increases in bortezomib above 1.3 mg/kg will be made.

Patients will be treated with bortezomib 1.3 mg/m² SQ on days 1, 4, 8, 11, 29, 32, 36, and 39 and temozolomide 75 mg/m²/day during radiation for 42 consecutive days. If there is myelotoxicity (ANC<1.5 or Plt<100) as determined on weekly blood draws, both

temozolomide and bortezomib will be held until (ANC>1.5 or Plt >100). One dose reduction will be allowed of bortezomib to 1.0 mg/ m² for the duration of the radiation phase. No dose reductions in temozolomide are permitted. If lower dose results in myelotoxicity (ANC<1.5 or Plt <100), treatment will be held until counts have recovered and resumed at this same lower dose. External beam fractionated regional radiation will be given on week days at 200 cGy doses to a total dose of 6000 cGy as specified in Appendix 8.12. The first post-radiation temozolomide cycle should be synchronized to within +/- two days of a bortezomib treatment. After a 2-6 week rest (two weeks preferred, but up to six weeks acceptable depending on toxicity) from temozolomide and bortezomib, following completion of radiation therapy, temozolomide will be restarted at 150 mg/m²/day for 5 days out of every 28. If there is myelotoxicity, dose reduction of both drugs will be planned as in below table. If the initial starting level is tolerated, subsequent cycles will be given at 200mg/m²/day. Bortezomib at 1.3 mg/m² will given on days 1, 4, 8, and 11 of a 28 day cycle commencing on the first day of temozolomide. Temozolomide will not be increased greater than 200 mg/ m²/day. Bortezomib will not be increased greater than 1.3 mg/m²/day. Assuming that the dosages of bortezomib and temozolomide are well tolerated, and no deterioration or treatment related toxicity sufficient to terminate study participation occurs, patients will then undergo clinical and radiographic tumor restaging and continue treatment for 24 additional 28 day cycles. If unacceptable toxicities after the first 12 cycles are observed per investigator's discretion, the bortezomib dosing schedule may be changed to 1.3 mg/m^2 weekly for 3 weeks on and 1 week off, with the possibility of further reduction if necessary to 1.3 mg/m^2 biweekly.

VELCADE Administration

Bortezomib will be given at 1.3 mg/m² SQ on days 1, 4, 8, 11, 29, 32, 36, and 39 during the 6 weeks of radiation. Bortezomib will be given at 1.3 mg/m² on days 1, 4, 8, and 11 of a 28 day cycle commencing on the first day of temozolomide for up to 24 cycles. Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). Patients may be treated on an out-patient basis, if possible.

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram (see section 8.3). The dose should be calculated using patient's baseline weight. If a patient experiences a notable change in weight (loss or gain of ≥10%) , then the patient's dose should be recalculated at that time and will become the new baseline weight.

There must be at least 72 hours between each dose of bortezomib.

INTRAVENOUS AND SUBCUTANEOUS ROUTE OF ADMINISTRATION HAVE DIFFERENT RECONSTITUTED CONCENTRATIONS. CAUTION SHOULD BE USED WHEN CALCULATING THE VOLUME TO BE ADMINISTERED.

SUBCUTANEOUS ADMINISTRATION:

Drug is available in sterile, single use vials containing 3.5 mg of bortezomib. Each vial of bortezomib for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with 1.4 mL of normal (0.9%) saline, Sodium

Chloride Injection USP, so that the reconstituted solution contains bortezomib at a concentration of 2.5 mg/mL for subcutaneous administration.

Subcutaneous Administration Precautions:

- The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.
- When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated.
- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.
- If local injection site reactions occur following bortezomib administration subcutaneously, a less concentrated bortezomib solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. Alternatively, the IV route of administration should be considered.
- In clinical trials of bortezomib IV, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

Temozolomide Admininstration

Temozolomide will be given at 75 mg/ m^2/day during radiation for 42 consecutive days. After a short holiday interval, temozolomide will resume at 150 mg/ m^2/day for 5 days out of every 28, and planned to be increased to 200 mg/ m^2/day. 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. Therefore, patients will be instructed to take temozolomide on an empty stomach, defined as not eating 1 hour before or 1 hour after drug administration.

3.3.3 Dose Modification and Delay

Radiation phase:

Temozolomide

No dose reductions in temozolomide are allowed during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMODAR dose should be continued throughout the 42-day concomitant period if all of the following conditions are met: absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, common toxicity criteria (CTC) non-hematological toxicity no greater then Grade 1 (except for alopecia, nausea, and vomiting), and no greater than Grade 2 for fatigue. During treatment a complete blood count including differential and platelets should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 5**. (Note: If temozolomide is interrupted or discontinued, bortezomib will be interrupted or discontinued as well.) PCP prophylaxis is required during the concomitant administration of TEMODAR and radiotherapy, and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC Grade 1).

Table 5		
Temozolomide Dosing interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide		
Toxicity	TMZ Interruption [a]	TMZ Discontinuation
Absolute Neutrophil Count	≥0.5 and <1.5 x 10^9/L	<0.5 x 10^9/L
Platelet Count	≥10 and <100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological toxicity (except for alopecia, nausea, vomiting, fatigue, and constipation)	CTC Grade 3 or intolerable Grade 2and at the investigators' discretion.	CTC Grade 4

[a] Treatment with concomitant TMZ may be continued when all of the following conditions are met: absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥ 100 x 10^9/L; CTC non-hematological toxicity ≤ Grade 2 (except for alopecia, nausea, vomiting, fatigue, and constipation).
TMZ- temozolomide; CTC = Common Toxicity Criteria

Bortezomib

If TMZ (and bortezomib) need to be interrupted per criteria in Table 5, resumption of TMZ at 75 mg/ m² and bortezomib at a lower dose (-1 dose reduction) will be allowed when toxicity recovers to an absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x10^9/L, or CTC non-hematologic toxicity ≤ Grade 2 (see Table 5). If counts require TMZ discontinuation, then bortezomib will also be discontinued for the duration of the radiation phase.

Radiation Phase:

Dose Level	Bortezomib (days 1, 4, 8, 11, 29, 32, 36, and 39)	Temozolomide (daily x 42 d)
-1	**1.0 mg/m²**	**75 mg/m²**
Starting	**1.3 mg/m²**	**75 mg/m²**

Maintenance (Post-radiation) phase:

Temozolomide and Bortezomib

Dosage of temozolomide in Cycle 1 (maintenance) is 150 mg/ m² once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/ m², if the CTC non-hematologic toxicity for Cycle 1 is Grade 2 (except for alopecia, nausea, vomiting, fatigue, or constipation), absolute neutrophil count (ANC) is ≥1.5 x 10^9/L, and the platelet count is ≥100 x 10^9/L. The dose remains at 200 mg/ m² per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. During treatment, a complete blood count with differential and platelets should be obtained on Day 22 (21 days after the first dose of TEMODAR) or within 72 hours (± 3 days) of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL).

The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Delay in treatment cannot exceed 4 weeks, and tumor must be stable. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to Tables 6 and 7. If further dose reductions are required, schedule should follow Table 9.

Temozolomide and bortezomib dosage will be recalculated during maintenance phase if there is a weight loss or gain of ≥10% of baseline weight. If this is required, then this weight used to recalculate the new dose will then be taken as the new baseline.

Table 6

Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
–1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 7

Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	$<1.0 \times 10^9$/L	See footnote b
Platelet Count	$<50 \times 10^9$/L	See footnote b
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

[a] TMZ dose levels are listed in **Table 6**.

[b] TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Table 8 Dosing Modification Table

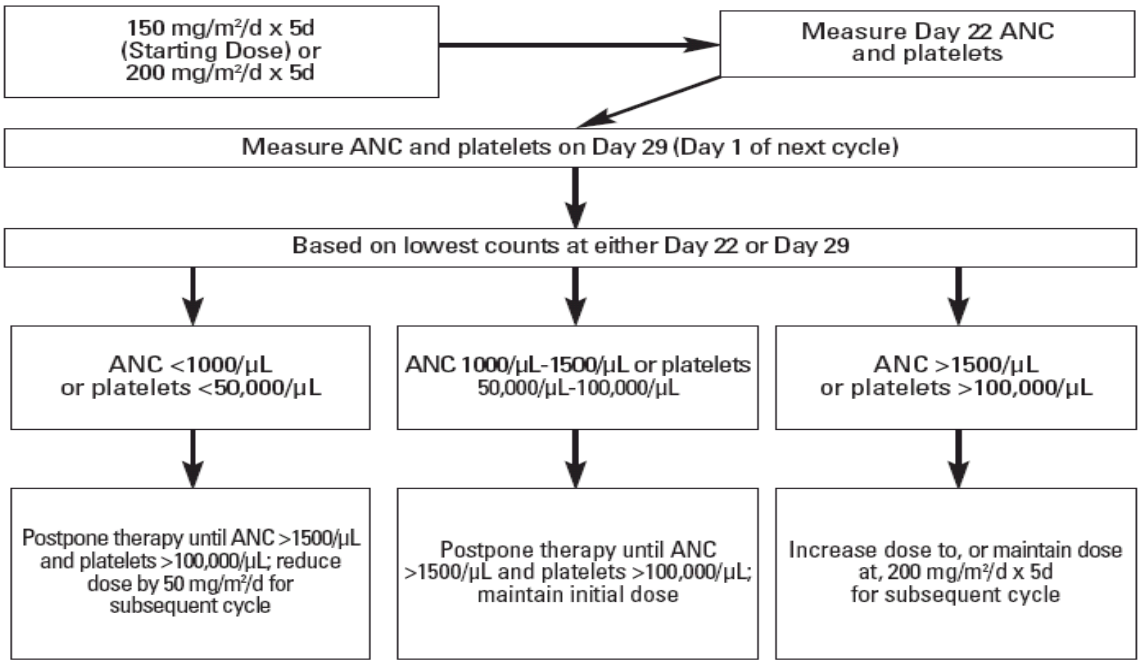

Table 9: Maintenance (Post-radiation) (28 day cycle):

Dose Level[a]	Bortezomib (days 1, 4, 8, and 11)	Temozolomide (day 1)
-3	1.0 mg/m^2	75 mg/ m^2
-2	1.0 mg/m^2	100 mg/ m^2
-1	1.3 mg/m^2	100 mg/m^2
Starting	1.3 mg/m^2	150 mg/m^2
+1	1.3 mg/m^2	200 mg/m^2

[a] Except for neuropathic pain, see Table 3.1 (bortezomib reduced to 0.7 mg/m^2)

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see section 8.6).

All previously established or new toxicities observed any time, with the exception of neuropathic pain and peripheral sensory neuropathy, are to be managed as follows:

If the patient experiences febrile neutropenia, a Grade 4 hematologic toxicity (including a platelet count $<25 \times 10^9$/L) or any ≥ Grade 3 non-hematologic toxicity considered by the investigator to be related to TMZ or VELCADE, then drugs are to be held.

For any ≥ Grade 3 non-hematologic toxicities, VELCADE is to be held for up to 2 weeks until the toxicity returns to Grade 1 or better.

Dose interruption or study discontinuation is **not** required for lymphopenia of any grade.

If, after VELCADE has been held, the toxicity does not resolve, as defined above, then drug must be discontinued.

Patients who experience VELCADE-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as presented in Table 3.1 Management of Patients with VELCADE-Related Neuropathic Pain and/or Peripheral Sensory Neuropathy.

Table 3-1 Management of Patients with VELCADE Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Recommended Dose Modification for VELCADE related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy	
Severity of Peripheral Neuropathy Signs and Symptoms	**Modification of Dose and Regimen**
Grade 1 (paresthesias, weakness and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce VELCADE by one dose level* If toxicity persists reduce by another one dose level. *
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold* VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg.m^2 and change treatment schedule to once per week.* If toxicity recurs, change treatment schedule to once every two weeks. *
Grade 4 (Sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis)	Discontinue VELCADE
Grading based on NCI Common Terminology Criteria CTCAE v3.0 NCI Common Terminology Criteria website - http://ctep.info.nih.gov/reporting/ctc.html	

ADL = activities of daily living
*Key:

Reduce by one dose level: VELCADE dose reduction from 1.3 to 1.0, or 1.0 to 0.7mg/m^2/dose.

Hold: Interrupt VELCADE until the toxicity returns to Grade 1 or better.

Schedule change: Schedule change from VELCADE twice per week (Days 1, 4, 8 and 11 on a Q4W cycle) to once per week (Days 1, 8, and 15 on a Q4W cycle).
Change from once per week to once every two weeks (Days 1, 15 on a Q4W cycle).

The neurotoxicity-directed questionnaire (see section 8.8) is a useful tool for determining the presence and intensity of neuropathic pain and/or peripheral neuropathy from the patient's perspective. Neuropathic symptoms are more prominent than abnormalities on the clinical examination. After the patient completes the neurotoxicity-directed questionnaire, the questionnaire should be reviewed to assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

Patients with mild hepatic impairment (bilirubin ≤ 1.5 × ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 -3.0 X ULN) while on study, the investigator should hold Bortezomib until the toxicity returns to < Grade 2. Restarting Bortezomib at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of Bortezomib-induced liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection and multiple myeloma-related liver disease.

3.3.4 Treatment Assignment
not applicable

3.3.5 Blinding, Packaging, and Labeling
VELCADE will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations.
Temozolomide will be obtained through the patient's pharmacy.

3.3.6 Concomitant Treatment

Concurrent Therapy

- Other Anti-cancer or Experimental Therapy: No other anti-cancer therapy (including chemotherapy, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other drug under investigation may be used concomitantly with the study drug. Patients are not allowed to participate concurrently in any other clinical study.
- Corticosteroids:Should be used in the smallest dose to control symptoms of cerebral edema and mass effect, and discontinued if possible.
- Anti-seizure medications: Should be used as necessary, however, since VELCADE is partially metabolized by inducers of CYP450 3A4 such as Enzyme-inducing anti-epileptic drugs (EIAED), patients on EIAED must be transitioned to non-EAIED at least 2 weeks prior to initiation of treatment.
- Antiemetics: Investigators will use their own discretion with regard to the appropriate treatment of nausea or vomiting.
- Anticoagulants: Patients who require treatment with full-dose warfarin or its equivalent (i.e., unfractionated and/or low molecular weight heparin) will NOT be removed from the study. Frequent monitoring of the INR is recommended.
- Growth Factors: Routine prophylactic use of G-CSF in the first course of therapy is *not* permitted, and secondary prophylaxis with G-CSF in subsequent courses is not generally recommended. Use of GM-CSF is not permitted at any time. However, prophylactic administration of G-CSF in a patient who is experiencing recurrent difficulties with neutropenia in subsequent cycles, or therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion.
- Other Concomitant Medications: Therapies considered necessary for the patient's well being may be given at the discretion of the investigator. On the day of VELCADE

administration, patients should not take any vitamin supplements such as Vitamin C, alpha lipoic acid, any antioxidant, or green tea. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications (prescription and OTC) must be recorded in the medical record and the case report forms.

- Potential drug interactions: Bortezomib has the ability to inhibit a variety of liver metabolic enzymes in vitro. The clinical impact of this inhibition in human taking drugs metabolized by these enzymes is unknown. Therefore, all patients enrolled onto this trial who are taking concomitant medications that are known to be metabolized by the liver should be closely observed for side-effects of these concomitant medications. (see Appendix 8.13 for the list of those medications)
- Febrile neutropenia: May be managed according to the local institution's Infectious Disease guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures, and the institution of broad-spectrum antibiotics. If a source for the fever is not identified, or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.
- Pneumocystis Pneumonia (PCP) prophylaxis:

  Since patients with malignant gliomas are at increased risk of developing PCP, especially if they are on corticosteroids, prophylaxis for PCP may be considered per institutional practice.
- Any investigational agent other than VELCADE is not permitted.

3.3.7 Treatment Compliance

All drug will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see section 8.3), and total drug administered in milliliters and milligrams. Any discrepancy between the calculated dose and dose administered, and the reason for the discrepancy, must be recorded in the source documents.

3.4 Duration of Treatment and Patient Participation

Patients will receive up to 24 28 day cycles of temozolomide and bortezomib after radiation therapy. All patients will be followed for survival. Patients who progress will be followed for survival every 4 months. Patients who complete therapy and do not progress should be followed every 2 months for 12 months, every 3 months for the next 12 months, every 4 months for the next 12 months, and then every 6 months until progression is determined. They should then be followed for survival every 4 months. Patients taken off study because of unacceptable toxicities will be followed up every 2 months until the toxicity is resolved or progression is determined by MRI.

3.5 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Intercurrent illness

- Occurrence of an unacceptable adverse event
- A treatment cycle delay or VELCADE and TMZ interruption of >4 weeks or missing three of four VELCADE doses within a treatment cycle because of toxicity
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

At the time of withdrawal, patients must have a physical exam, a neurological exam, urine tests and routine blood tests. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

3.6 Efficacy, Pharmacodynamic/Pharmacogenomic/Correlative studies, and Safety Measurements

3.6.1 Efficacy Measurements

3.6.1.1 Primary Efficacy Variables:
Overall Survival

3.6.1.2 Secondary Efficacy Variables:
12-month survival and median time to tumor progression tumor response as assessed by MRI and neurologic exam, toxicity.

The patients will have a brain MRI evaluation of response and progression every 8 weeks, starting from the day 56 scan obtained 2 weeks after completion of radiation and daily temozolomide. MRI assessment will be conducted on a 7-point scale. This scale is expected to be more useful in this study because many newly-diagnosed patients are likely not to have evaluable disease due to gross total resections. A -2 or -3 assessment will be taken as progression. Determination of whether progression occurs based on the day 56 scan will take into account the untreated window between baseline MRI and day of 1 of the study.

complete resolution of tumor: 3
tumor definitely smaller: 2
tumor probably smaller: 1
tumor unchanged: 0
tumor probably worse: -1
tumor definitely worse: -2
new lesion: -3

Neurological Exam: Although not used for determining response, it is useful to evaluate improvement in the neurologic exam that should coincide with objective

measurement of tumor size.

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse
B	Baseline

Performance Status, Neurological Function, and Mental Status: Patients will be graded according to Karnofsky Performance Status (see Appendix 8.2), Neurological Function and Mental Status.

Time to Treatment Failure: From date of registration to the date of first observation of progressive disease, non-reversible neurologic progression, or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment.

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

Molecular Analysis: Pre-treatment biomarker data (MGMT promoter methylation and IDH1 genotype) will be analyzed and descriptive statistics will be generated. Analyses of a graphical nature comparing the biomarker data with the best overall response (CR, PR, SD, PD) are also planned.

3.6.2 Pharmacokinetic/Pharmacodynamic/Pharmacogenomic/Correlative Studies

[redacted]

[redacted]

3.6.3 Safety Measurements

Toxicity/safety: Patients will be assessed using CTC 3.0 for Grade 3 or greater treatment related non-hematologic toxicities.

4 ADVERSE EVENTS

All serious adverse events (SAEs) (regardless of expectedness, causality, and whether commercial or investigational bortezomib is used) must be reported to Millennium Pharmacovigilance (or designee). See Section 4.2 for the reporting of SAEs.

The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

4.1 Definitions

4.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

4.1.2 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening**. (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. (see clarification below on planned hospitalizations in Section **Error! Reference source not found.**).
- 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 a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. 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; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

4.2 Procedures for AE and SAE Reporting

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common

underlying pathology should be noted as one comprehensive event. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of bortezomib up to and including 30 days after administration of the last dost of bortezomib. Any SAE that occurs at any time after completion of bortezomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). 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).

Since this is an investigator-initiated study, the principal investigator [redacted], also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB. Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported to Millennium Pharmacovigilance.

Fatal and Life Threatening SAEs within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The protocol may include language to specify expected adverse events which will not be considered serious and will not require expedited reporting.

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study products as soon as possible but no later than 4 calendar days of such communication.

SAE and [redacted]

Suggested Reporting Form:

- SAE Report Form (a sample is provided in Appendix **Error! Reference source not found.**)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

4.3 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 4.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 4.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form: Pregnancy Report Form (Appendix 8.15)

5 STATISTICAL PROCEDURES

5.1 Sample Size Estimation

The sample size calculation for this one-arm trial is based on an endpoint of 18-month survival rate with a 36-month accrual period (1-2 patients/month). The following assumptions are made: 1. Survival time follows an exponential distribution, 2. The 18-month survival rate is 55% (median survival 21 months) for the new treatment and 40% (median survival 14 months) for the standard treatment (based on (Stupp, Mason et al. 2005), 3. The 18-month survival rate is estimated using the Kaplan-Meier method, 4. Test statistics – Z-test, Type I error=0.05, 5. N=50 (total patients). In a performed simulation, the power is 70% for 1-sided test.

5.2 Randomization and Stratification

Not applicable

5.3 Populations for Analysis

This study will be a multi-center, open-label, phase II study assessing safety and efficacy in adult newly-diagnosed GBM patients that have had no prior therapy other than surgery. This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Males and females will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will actively be recruited to participate.

5.4 Procedures for Handling Missing, Unused, and Spurious Data

All data will be stored in the patient's medical record and duplicates or research specific CRFs in their research records. We will only be collecting data that is relevant for this study. All unused data will be stored per medical records policy and procedures for handling of medical records.

5.5 Statistical Methods

5.5.1 Baseline Comparisons

The primary endpoint will be total survival from the date of surgical-pathological diagnosis. For the final analysis, results will be compared with the results on comparable patients whose data are available through the UCLA Neuro-oncology Department database. These comparable patients were all newly diagnosed GBM patients who were treated on research protocols and similar to the patients in the present study insofar as they will be patients seen at a tertiary center and enrolled into clinical trials early after diagnosis. The primary analysis will utilize a Cox proportional hazards model including age, KPS, and extent of resection. This allows for adjustment for major prognostic factors.

5.5.2 Efficacy Analysis

Primary Efficacy Variables

Overall Survival

Secondary Efficacy Variables

12-month survival and median time to tumor progression tumor response as assessed by MRI and neurologic exam, toxicity.

The patients will have a brain MRI evaluation of response and progression every 8 weeks, starting from the day 56 scan obtained 2 weeks after completion of radiation and daily temozolomide. Assessment will be conducted on a 7-point scale. This scale is expected to be more useful in this study because many newly-diagnosed patients are likely not to have evaluable disease due to gross total resections. A -2 or -3 assessment will be taken as progression. Determination of whether progression occurs based on the day 56 scan will take into account the untreated window between baseline MRI and day of 1 of the study.

complete resolution of tumor: 3
tumor definitely smaller: 2
tumor probably smaller: 1
tumor unchanged: 0
tumor probably worse: -1
tumor definitely worse: -2
new lesion: -3

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

+2	Definitely better
+1	Possibly better
0	Unchanged
-1	Possibly worse
-2	Definitely worse
B	Baseline

Performance Status, Neurological Function, and Mental Status: Patients will be graded according to Karnofsky Performance Status**,** Neurological Function and Mental Status (see Appendix 8.2).

Time to Treatment Failure: From date of registration to the date of first observation of progressive disease, non-reversible neurologic progression or permanently increased steroid requirement (applies to stable disease only), death due to any cause, or early discontinuation of treatment.

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

Molecular Analysis: Pre-treatment biomarker data (MGMT and IDH1) and additional correlative markers will be analyzed and descriptive statistics will be generated. Exploratory analyses of a graphical nature comparing the biomarker data with the best overall response (CR, PR, SD, PD) are also planned.

5.5.3 Safety Analysis

The PI will be responsible for accurate, consistent, timely, complete, and reliable data collection.

The study coordinator and PI are responsible for ensuring that the following forms are completed in a legible and timely manner for every patient enrolled on study. These forms are an integral part of the study data and will be maintained in the patient's clinical chart at UCLA. Errors on the forms should be lined through, but not obliterated with the correction inserted, initialed and dated by the study coordinator or PI. These forms will be available at all times for inspection by the FDA and UCLA.

Registration Form
On-study Eligibility Checklist
UCLA Adverse Event Form
MedWatch Form (Form 3500)

In addition to the patient data maintained on the forms listed above, patient data will also be entered into a Microsoft Excel spreadsheet or database. The data are backed up daily and stored on a secure medical center server. The PI, study investigators and data coordinator for the study are the only individuals who will have access to the password-protected data file.

Quality assurance measures are provided by three mechanisms: 1) ongoing monitoring of protocol compliance, 2) on-site audits, and 3) response reviews. Monitoring will begin at the time of patient registration and will continue during protocol performance and completion. This trial is subject to Cancer Center Internal Quality Assurance Monitoring.

Data and the progress of this trial will be reported to the DSMB at regular intervals as determined by the DSMB. The first data summary report will be due quarterly, starting from the date of the IRB approval.

JCCC DSMB

This trial is subject to the Jonsson Comprehensive Cancer Center Internal Quality Assurance program.

The JCCC Data and Safety Monitoring Board (DSMB) meets monthly to review all serious adverse event reports for trials overseen by the JCCC DSMB. All serious adverse event (SAE) reports, which have been filed since the previous meeting, are presented to the committee for review.

For all trials where the JCCC DSMB has primary oversight for SAE review, all SAEs occurring within these studies shall be reported to the JCCC DSMB in a timely manner consistent with the UCLA IRB time requirements [ten days, two days for a death] regardless of relationship, expectedness or severity. The JCCC Office of Regulatory Compliance (ORC) will review all submissions and the ORC staff will enter the information into the JCCC Clinical Trials database. Reports are generated for full JCCC DSMB review of those SAEs that have some component of relatedness to the study drug and may, at the discretion of the JCCC compliance officers, include SAE reports that may require DSMB review. For trials where the JCCC DSMB has primary DSMB review responsibility, the DSMB will

request that the PI generate cumulative adverse event reports for quarterly, biannual or annual review.

The DSMB reviews each SAE report and determines whether or not protocol modifications are warranted to ensure subject safety. In this review, prior occurrences of similar toxicity with the therapy under study are taken into consideration, as well as the servity of the event and the likelihood that it was related to a study drug. The DSMB may recommend no changes to the study if the event is expected or related to other causes such as the subject's underlying condition. The DSMB may request an expert's advice of another non-Principal Investigator with national experience to support their deliberations and decisions. The JCCC DSMB has the authority to recommend to the UCLA IRB the immediate halt to the study (i.e., discontinuation of any further treatment of enrolled subjects and discontinuation of enrollment of new subjects) should there be any serious unexpected toxicity that warrants further investigation. JCCC DSMB correspondences are addressed to the Principal Investigator and copied to the UCLA IRB. Minutes of the DSMB meetings are recorded and processed into the computer file.

Monitoring, Auditing and Reporting

The NIH and NCI policy statements allow for variable monitoring and reporting plans, commensurate with the potential risks and with the size and complexity of the trial. The monitoring plan must be sufficiently rigorous and effective to ensure subject safely and to ensure protocol compliance and data validity and integrity.

Level of Risk of a Study

All interventional clinical trials undergo scientific review by the Internal Scientific Peer Review Committee (ISPRC) which requires that a Data and Safety Monitoring Plan is in place before a trial can be approved to begin. For trials overseen by the JCCC DSMB, the JCCC DSMB will determine the degree of risk of the study and will ensure that there are procedures in place to ensure the safety of the subjects that are enrolled in the trial. The intensity level of the monitoring is determined by the risk category. Some of the factors that must be considered when assigning the Level of Risk category include:

1. A biostatistical design and appropriate procedures for proper data management so that the information collected can be properly validated.
2. Appropriate Serious Adverse Event reporting procedures must be in place.
3. The study duration must be appropriate and must be based on a realistic rate of enrollment.
4. Data collection and data management must be adequate to verify and ensure subject eligibility.

Assignment of risk

Assigning risk ensures that the data and safety monitoring is based on the level of risk (low, medium, or high) to ensure that the data and safety monitoring activities are appropriate. Below are some of the criteria used to make a decision regarding the assignment of risk:

- Expected duration of the study based upon the estimated rate of enrollment.
- Type of study population (e.g., children, geriatric)
- The procedures used in the trial are commensurate with the degree of risk.
- Adequate data management systems in place and appropriate case report forms

- Proper serious adverse event reporting procedures in place
- Proper biostatistical design and data analysis procedures in place.

Level of Risk

Level 2

Example of type of trial:
Institutional study for which IND is exempt by FDA. Examples are studies using commercially available agents for an unapproved indication based on standard regimen.

1. Compliance Officer meets with PI/Staff prior to study initiation; review regulatory requirements and operating system. Compliance Officer provides real time monitoring to determine eligibility prior to enrollment onto the protocol.
2. Real time QA monitoring of the subjects and data collection occurs for all subjects entered onto the trial.
3. Comprehensive QA auditing within first year or first 10 subjects enrolled, whichever comes first. Subsequent audit frequency will be annually.
4. Frequency of DSMB Summary Report is typically on a biannual basis or approximately every six months.

Monitoring and Auditing Activities

The compliance officer of the JCCC Office of Regulatory Compliance [ORC] will monitor the clinical records for all human subjects enrolled onto JCCC trials overseen by the JCCC DSMB. The JCCC compliance officer will perform real time review of informed consent processes and the meeting of all inclusion and exclusion criteria and screening results at study entry. Active monitoring will offer the JCCC study teams prospective information that can be used to enhance the quality of research being performed contemporaneously. Auditing is a review of historic performance of the research effort and is performed on case report forms, regulatory files and source documents to measure the quality of the research effort in a retrospective manner.

This study will be conducted at UCLA Medical Center and Columbia University Medical Center. The study will be monitored by the UCLA JCCC Quality Assurance Program and they may perform audits of the Columbia University Medical Center if deemed necessary. In addition, a monthly team conference will be done among study investigators from all external network study sites during which toxicity data including all SAEs will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome and compliance with study guidelines.

The PI will be responsible for ensuring that study monitoring requirements are met. Upon request the monthly safety meeting agenda will be submitted also to the UCLA JCCC Quality Assurance Program. The quality control procedure of data and protocol adherence will be performed through a site visit and/or teleconference at external network study sites by the study coordination center personnel from the UCLA Neuro-Oncology Center at least once a year. Copies of all monitoring and audit reports at external study sites will be provided to UCLA JCCC DSMB.

5.5.4 For this multi-center clinical trial, the following organizations are involved in the [redacted]

[redacted]

All clinical sites are responsible for the recruitment, treatment, and evaluation of patients with newly diagnosed brain tumor who meet eligibility criteria. Each site will include one or more responsible physicians/ investigators, and a study coordinator. The investigator and coordinator from the study coordination center, UCLA Neuro-Oncology Program, who represents the institution, will provide oversight of the following procedures at external network study sites including eligibility verification.

- Eligibility Screening: FAX a copy of the eligibility checklist form and registration form to [redacted] review and verification of eligibility. No exemption will be granted for any study entry at external network sites without prior approval by the PI.

- Clinical evaluation: all data will be captured and recorded on the case report forms provided. The quality control procedure of data and protocol adherence will be performed through a site visit to each network site by study coordination center personnel from UCLA Neuro-Oncology Center. Study oversight will begin at the time of subject registration and will continue during protocol performance and completion. Monthly safety meeting will take place in order to review of currently enrolled patients at each site.

- Data Management: updating and maintenance of case report forms and subjects files, solving the data queries, updating and maintenance of subject's status log, reporting all SAEs occurring at sites.

    a) The above referenced study will have an externally constituted safety monitoring group. In addition, external sites have their own DSMB plans.

    b) Safety data is reviewed on a continual basis as adverse events and reports of toxicities, laboratory findings and reports of Serious Adverse Events are received.

    c) Serious adverse events are reported to the main coordination center using

specific forms provided to the sites. Upon receipt of a report, the Medical Monitor will review the event or toxicity and forward the information with comments or recommendations to the Principal Investigator at each site. Documents consists of a cover letter and corresponding safety report(s) will be sent via e-mail attachments within five working days from the date the documents.

If required, the Medical Monitor from U[redacted] will confer with the Principal Investigator at the site reporting the event to determine a course of action regarding patient treatment, dose modification or suspension of patient treatment. Main coordination center will report to the FDA, a narrative will be prepared by the Medical Monitor and forward all MedWatch Form FDA 3500A to the participating sites, and the manufacturer of the study drug, Millennium Pharmaceuticals, Inc.

d) Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and Serious Adverse Events (SAEs); measurement of protocol-specified tumor progression, laboratory results, clinical examination; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug. All study-related safety data will be collected until 30 days after the last dose of study drugs. Survival status will be collected every 4 months until death.

5.5.5 Correlative studies

[redacted]

5.6 Interim Analysis

After 10 patients with newly-diagnosed GBM are treated, an interim analysis will be conducted. If 3 or more patients have experienced unacceptable toxicity (defined as grade 4 non-hematologic toxicity or any grade 5), enrollment will be suspended pending full assessment of safety risks to determine if the study should continue. Otherwise, patient accrual will continue.

5.7 Procedures for Reporting Deviations to Original Statistical Analysis Plan

All deviations will be reported to our local IRB as they occur and on an annual basis per standard procedures for reporting.

6 ADMINISTRATIVE REQUIREMENTS

6.1 Product Complaints

A product complaint is a verbal, written, or electronic expression which implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see the following) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact MedComm Solutions (see below) and report the event.

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 4.2).

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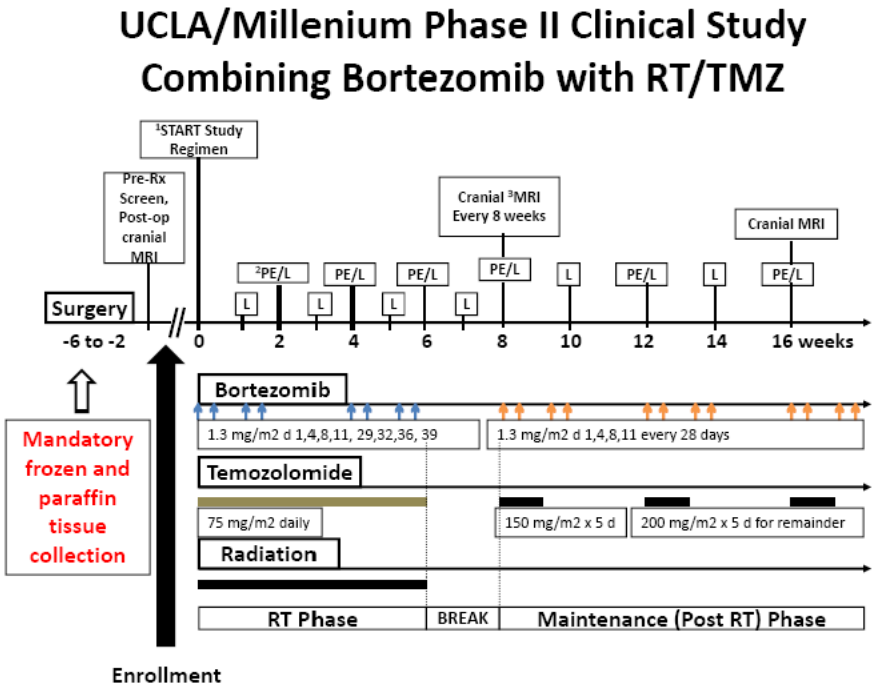
8 APPENDICES

8.1 Study Flow Chart



ELIGIBILITY
- Newly-diagnosed glioblastoma
- 2-6 wks from surgery
- Other eligibility criteria (Section 5.0)

[1]Study Regimen: Bortezomib is given subcutaneously at 1.3 mg/ m^2 on days 1, 4, 8, 11, 29, 32, 36, and 39 during radiation as early as 14 days after surgery. Temozolomide is given daily (75mg/m^2) during radiation, followed by 5 days out of 28 for 24 additional cycles. The dose is 150-200 mg/m2 on those days. Bortezomib at 1.3 mg/m^2 is given on days 1, 4, 8, and 11 of each subsequent 28 day cycle. Both bortezomib and temozolomide will continue until progression or up to 24 cycles.

[2]PE/L – physical examination on day 28 of every cycle and at study discontinuation. Laboratory blood testings weekly during radiation and every cycle thereafter.

[3]MRI – at baseline screening within 21 days of day 1; then at day 56; then every 2 cycles (56 days +/- 3 days)

8.2 Karnofsky Performance Status Scale (The following table presents the Karnofsky performance status scale[1])

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
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/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

NEUROLOGICAL FUNCTION – CIRCLE ONE

DESCRIPTION
0 **N**o neurologic symptoms; fully active at home/work without assistance **1** **M**inor neurologic symptoms; fully active at home/work without assistance **2** **M**oderate neurologic symptoms; fully active at home/work but requires assistance **3** **M**oderate neurologic symptoms; less than fully active at home/work and requires assistance **4** **S**evere neurologic symptoms; totally inactive requiring complete assistance at home or institution; unable to work

MENTAL STATUS – CIRCLE ONE

DESCRIPTION
0 **N**ormal function **1** **M**inor mental confusion **2** **G**ross confusion but awake **9** **U**nknown

[1] Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984; 53:2002-2007.

8.3 Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using the DuBois (preferable) or the Mosteller formula.

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{\text{(140-age) (actual wt in kg)}}{\text{72 x serum creatinine (mg/dl)}}$$

For females use 85% of calculated CrCl value.

Note: In markedly obese patients, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

8.4 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

8.5 Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality

of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
2. The benefits, risks, burdens and effectiveness of a new method should be tested against

those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

8.6 Common Terminology Criteria for Adverse Events Version 3.0

http://ctep.cancer.gov/reporting/ctc.html

8.7 RTOG/EORTC Late Radiation Morbidity Scoring Scheme

RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Use for toxicity occurring greater than 90 days after radiation therapy.

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bladder- Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency / generalized telangiectasia / intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc) / severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus - Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis / perforation ; fistula
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis / complete fixation
Kidney- Late RT	No change from	Transient albuminuria; no	Persistent moderate	Severe albuminuria;	Malignant hypertensi

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Morbidity Scoring	baseline	hypertension; mild impairment of renal function; urea 25-35 mg%; creatinine 1.5-2.0 mg%; creatinine clearance >75%	albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36–60 mg%; creatinine clearance >50-74%	severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	on; uremic coma / urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis / hepatic coma or en-cephalopa thy

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency / continuous O_2 / assisted ventilation
Mucous membrane - Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis / perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthal-mitis; blindness
Radiation- Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

8.8 FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

FACT/GOG-Neurotoxicity Questionnaire, Version 4.0

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
I have numbness or tingling in my hands……	0	1	2	3	4
I have numbness or tingling in my feet……	0	1	2	3	4
I feel discomfort in my hands……	0	1	2	3	4
I feel discomfort in my feet……	0	1	2	3	4
I have joint pain or muscle cramps……	0	1	2	3	4
I feel weak all over……	0	1	2	3	4
I have trouble hearing……	0	1	2	3	4
I get a ringing or buzzing in my ears……	0	1	2	3	4
I have trouble buttoning buttons……	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand……	0	1	2	3	4
I have trouble walking……	0	1	2	3	4

Sources: Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79.

8.9 Sample Collection and Handling Requirements; 20S Proteasome Inhibition Assay

Not applicable.

8.10 Sample Collection and Handling Requirements; PK

Not applicable.

8.11 Sample Collection and Handling Requirements; PGx

Not applicable.

8.12 RADIATION THERAPY GUIDELINES

Source of guidelines

The information that follows is adapted from current guidelines of the Radiation Therapy Oncology Group (RTOG) for standard radiotherapy for glioblastoma in the clinical trial setting. Much of the text is quoted directly, with permission.

Dose Definition and Schedule

Radiotherapy must begin within 35 days (5 weeks) of surgery. One treatment of 2.0 Gy will be given daily 5 days per week for a total of 60.0 Gy over six weeks. Treatment may be omitted on holidays, resulting in slight extension of the total period of treatment. All portals shall be treated during each treatment session. Treatment with a single beam is not acceptable due to unacceptable tumor dose inhomogeneity.

Target dose definition

Dose is specified as the target dose, which shall be the dose to the center of the target volume. For the following portal arrangements the target dose shall be specified as follows:

For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

For complete rotation or arc therapy: in the plane of rotation at the center of rotation.

The technique of using two opposing co-axial unequally weighted fields is not recommended due to unacceptable hot spots and unacceptable dose inhomogeneity. However, if this technique is utilized, the dose shall be specified at the center of the target area.

Other or complex treatment arrangements: at the center of the target volume.

Physical Factors

Treatment shall be delivered with megavoltage machines of energy ranging from Cobalt 60 up to and including 10 MV photons. Selection of the appropriate photon energy*(ies)* should be based on optimizing the RT dose distribution within the target volume and minimizing dose to non-target normal tissue. Photon energies > 10 MV should be utilized only in dual energy beam arrangements using at least one beam with energy $\leq$ 10 MV. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Source sizes must be no more than 2 cm in Cobalt 60 machines. For Cobalt 60 machines, secondary collimation is required. Boost with electrons, particles, stereotactic radiosurgery, or implants is not permissible.

Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device that is transparent to x-rays must ensure adequate immobilization during therapy and ensure reproducibility. The target volume for both the initial volume and the conedown volume shall be based on the preoperative MRI/CT. The initial target volume shall include the contrast-enhancing lesion and surrounding edema *(if it exists)* demonstrated on MRI/CT plus a 2.0 centimeter margin. If no surrounding

edema is present, the initial target volume should include the contrast-enhancing lesion plus a 2.5 centimeter margin.

This initial target volume will be treated to 46.0 Gy in 23 fractions. After 46 Gy the conedown tumor volume should include the contrast enhancing lesion *(without edema)* on the pre-surgery MRI/CT scan plus a 2.5 centimeter margin.

Treatment Planning

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. MRI/CT-guided treatment planning is necessary to assure accuracy in the selection of field arrangements.

Isodose distributions for the initial target volume and the conedown target volume are required on all patients, including those treated with parallel opposed fields. A composite plan is required showing the respective target volumes. The inhomogeneity across the target volume shall be kept to a minimum.

The minimum dose to the target volume should be kept within 5% of the dose at the center of the volume. The maximum dose should be no higher than 5% of the dose at the center of the target volume.

Dose Limitations to Critical Structures

The lens and cervical spine must be shielded from the direct beam at all times. When possible to do without shielding gross tumor, attempts should be made to limit the dose to the optic chiasm to 60 Gy, the retina of at least one eye (but preferably both)to 50 Gy, and the brain stem to 60 Gy.

Documentation Requirements

A copy of the pretreatment MRI/CT, the treatment prescription form, treatment calculation form, simulation films and representative portal films of each initial field must be available to be provided on request to the principal investigator. At the completion of treatment, the following must also be available on request*:* daily treatment record, all isodose distributions, simulation and portal films of the reduced fields, and the radiotherapy summary.

8.13 Drugs known to be metabolized by CYP450 isoenzyme 3A4

CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	Diazepam (minor; hydroxylation, N-demethylation)
Carbamazepine	
Cevimeline	Nefazodone
Cerivastatin	Nelfinavir
Digitoxin	Nevirapine
Diltiazem	Nicardipine
Disopyramide	Nifedipine
Docetaxel	Niludipine
Dolasetron	Nimodipine
Donepezil	Nisoldipine
Doxorubicin	Nitrendipine
Doxycycline	Omeprazole (sulfonation)
Dronabinol	Ondansetron
Enalapril	Oral contraceptives
Erythromycin	Orphenadrine
Estradiol	Paclitaxel
Ethinyl estradiol	Pantoprazole
Ethosuximide	Pimozide
Etoposide	Pioglitazone
Exemestene	Pravastatin
Dofetilide (minor)	Prednisone
Felodipine	Progesterone
Fentanyl	Proguanil
Fexotenadine	Propafenone
Finaxteride	Quercetin
Fluoxetine	Quetiapine
Flutamide	Quinidine
Glyburide	Quinine

Granisetron	Repaglinide
Halofantrine	Retinoic acid
Hydrocortixone	Rifampin
Hydroxyarginine	Risperidone
lfosfamide	Ritonavir
lmipramine	Salmeterol
lndinavir	Saquinavir
lsradipine	Sertindole
ltraconazole	Sertraline
Ketoconazole	Sibutramine
Lansoprazole (minor)	Sildenafil citrate
Letrozole	Simvastatin
Levobupivicaine	Sirolimus
Lidocaine	Sufentanil
Loratadine	Tacrolimus
Losartan	Tamoxifen
Lovastatin	Temazepam
Methadone	Teniposide
Mibefradil	Terfenadine
Miconazole	Testosterone
Midazolam	Tetrahydrocannabinol
Mifepristone	Theophylline
Mirtazapine (N-demethylation)	Tiagabine
Montelukast	Tolterodine
Navelbine	Vincristine
Toremifene	Warfarin (R-warfarin)
Trazodone	Yohimbine
Tretinoin	Zaleplon (minor pathway)
Triazolam	Zatoestron
Troglitazone	Zileuton
Troleandomycin	Ziprasidone
Venlafaxine (N-demethylation)	Zolpidem
Verapamil	Zonisamide
Vinblastine	
Inducers	
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Ethosuximide	Progesterone
Glucocorticoids	Rifabutin
Griseofulvin	Rifampin
Nafcillin	Rofecoxib (mild)
Nelfinavir	St John’s wort
Nevirapine	Sulfadimidine
Oxcarbazepine	Sulfinpyrazone
Phenobarbital	Troglitazone
Phenylbutazone	
Inhibitors	
Amiodarone	Ketoconazole
Anastrozole	Metronidazole
Azithromycin	Mibefradil
Cannabinoids	Miconazole (moderate)
Cimetidine	Nefazodone
Clarithromycin	Nelfinavir
Clotrimazole	Nevirapine

Cyclosporine	Norfloxacin
Danazol	Norfluoxetine
Delavirdine	Omeprazole (weak)
Dexamethasone	Oxiconazole
Diethyldithiocarbamate	Paroxetine (weak)
Diltiazem	Propoxyphene
Dirithromycin	Quinidine
Disulfiram	Quinine
Entacapone (high dose)	Quinupristin and dalfopristin
Erythromycin	Ranitidine
Ethinyl estradiol	Ritonavir
Fluconazole (weak)	Saquinavir
Fluoxetine	Sertindole
Fluvoxamine	Sertraline
Gestodene	Troglitazone
Grapefruit juice	Troleandomycin
lndinavir	Valproic acid (weak)
lsoniazid	Verapamil
ltraconazole	Zafirlukast
	Zileuton

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)