Thomas Jefferson University

THOMAS JEFFERSON UNIVERSITY
Kimmel Cancer Center

PHASE I STUDY OF ALISERTIB WITH CONCURRENT FRACTIONATED STEREOTACTIC RADIATION TREATMENT FOR RECURRENT HIGH GRADE GLIOMAS

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List of Abbreviations

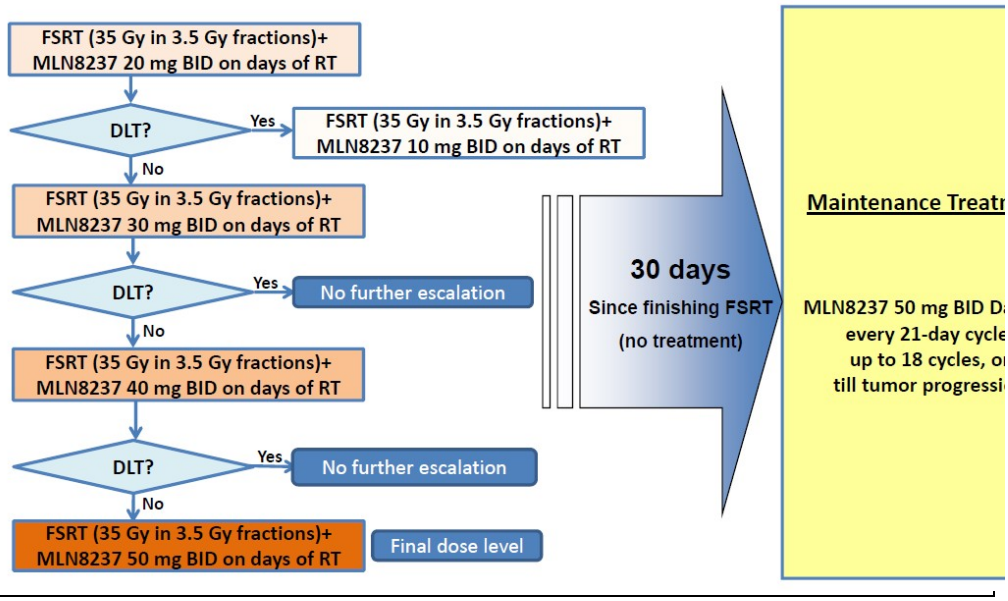
AE	**adverse event**
ALT	**alanine aminotransferase/glutamic pyruvic transaminase/GPT**
ANC	**absolute neutrophil count**
ASCO	**American Society of Clinical Oncologists**
AST	**aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT**
AUC	**area under the curve**
BUN	**blood urea nitrogen**
CIS	**carcinoma in-situ**
Cmax	**maximum concentration of drug**
CNS	**central nervous system**
CR	**complete response/remission**
CTCAE	**NCI common terminology criteria for adverse events**
CV	**coefficient of variation**
DLT	**dose-limiting toxicity**
DNA	**deoxyribose nucleic acid**
ECG	**12 lead electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
FDA	**food and drug administration**
GBM	**Glioblastoma**
Gy	**Gray (unit of radiation)**
H3, H4	**histones H3, H4**
HIV	**human immunodeficiency virus**
i.v.	**intravenous(ly)**
IRB	**institutional review board**
LLN	**lower limit of normal**
LVEF	**left ventricular ejection fraction**
mg/m2	**milligrams per square meter**
MTD	**maximum tolerated dose**
MUGA	**multiple uptake gated acquisition scan**
MWF	**monday, wednesday, Friday**
NCI	**national cancer institute**
NHL	**non-hodgkin's lymphoma**
NIH	**national institutes of health**
PD	**Pharmacodynamic**
P-gp	**p-glycoprotein**
PK	**Pharmacokinetic**
PLT	**Platelet**
PR	**partial response**
SAE	**serious adverse event**
QoL	**Quality of life**
SD	**stable disease**
FSRT	**Fractionated stereotactic radiation therapy**
T4	**Thyroxine**
TSH	**thyroid stimulating hormone**

ULN	**upper limit of normal**
WBC	**white blood cell**
WNL	**within normal limits**
WOCBP	**women of childbearing potential**

Study Summary

Title	Phase I study of Alisertib with concurrent fractionated stereotactic radiation treatment for recurrent high grade gliomas
Short Title	Safety study of Alisertib and radiation for recurrent glioma
Protocol Number	JeffTrial# 3007 CCRRC# 2013-12 IRB# 13P.528
Phase	1
Methodology/Study Design	This is an open label phase I clinical trial. Alisertib will be administered twice daily by mouth on days of radiation treatment. The radiation dose and fractionation are pre-determined. Alisertib dose will escalate according to the protocol. There is no intra-patient dose escalation.
Study Duration	18 months
Study Center(s)	Single-center.
Objectives	**Primary Objectives**: 1. Evaluate the safety and tolerability of the study treatment 2. To determine the Maximum Tolerated Dose (MTD) of Alisertib when combined with fractionated stereotactic radiation treatment for recurrent high grade glioma. **Secondary Objectives:** 1. To estimate 6 month progression free survival rate 2. To estimate the median time to progression 3. To estimate overall survival 4. To estimate the impact on quality of life (QoL)
Number of Subjects	Up to 24 subjects

Diagnosis and Main Inclusion Criteria	Patients with recurrent high grade glioma (grade III or IV). Main inclusion criteria: 1. Patients must have a previously histologically or cytologically confirmed high grade glioma (astrocytic or oligodendroglial supratentorial tumors grade 3 or 4) that has been previously treated with fractionated radiation therapy and now shows evidence of recurrence. 2. Patients must have recovered from the toxic effects of prior therapy. 3. Patients must have recovered from the effects of surgery. There must be a minimum of 21 days from the day of surgery to the day of protocol treatment. For core or needle biopsy, a minimum of 7 days must have elapsed prior to the day of protocol treatment. 4. Prior treatment with cytotoxic and biological agents is permissible. There should be at least a 2-week break between prior treatment and the protocol treatment. 5. Prior treatment with fractionated radiation therapy (up to 60Gy) is an eligibility criterion, however there should not have been a second course of fractionated radiotherapy to the supratentorial area. 6. One prior single fraction radiosurgical procedure within the treatment field is acceptable if V12<5 cc (V12 is the volume of normal brain (outside GTV) receiving 12 or more Gy). Additional radiosurgical procedures outside of the treatment area are acceptable. 7. Subject must be able to take oral medication and to maintain a fast is required for 2 hours before and 1 hour after MLN8237 administration. 8. ANC > 1500/mm³, platelets > 100,000/mm³, Hgb > 9 g/dL. Values must be obtained without need for myeloid growth factor or platelet transfusion support within 14 days of registration. However, erythrocyte growth factor is allowed as per published ASCO guidelines. 9. Total bilirubin ≤ ULN, SGOT (AST) and SGPT (ALT)< 1.5 x ULN, within 14 days of registration. 10. clearance m -Gault), within 14 days of registration. 11. Age >18 years. 12. ECOG performance status <2 (see Appendix I). 13. Life expectancy of greater than 2 months. 14. Women of childbearing potential must have a negative β-HCG pregnancy test documented within 7 days prior to registration. 15. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for 4 months after last dose. 16. Ability to understand and the willingness to sign a written informed consent document.

Study Therapy, Dose, Route, Regimen	Alisertib (MLN8237) will be administered by mouth, twice daily. The dose of Alisertib will be defined by the protocol.
Duration of administration and follow-up	Concurrent with radiation treatment, then 30 days after finishing radiation therapy will receive twice daily from day 1-7, every 21 day cycle for up to 18 cycles, or until tumor progression.
Reference therapy	None. This is a phase I study
Statistical Methodology	We will use a two-stage accrual design at each dose considered. We will initially enter 3 subjects at each dose. If none of the three experiences a dose-limiting toxicity we will proceed to the next dose. If one of the three experiences toxicity at that level, we will accrue 3 more subjects at that dose. If at any time there are two or more dose-limiting toxicities (in the 3-6 subjects) on a given dose, we will terminate accrual to the Phase I portion of that trial. No patient will be treated at a higher dose until the 3 or 6 patients have completed their toxicity evaluation period at the current dose. With this plan, a dose with a 50% or greater probability of causing a dose-limiting toxicity has at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and at least a 50% chance of stopping at 3. With the two-stages (3-6) together, there is at most a 17.2% chance of escalation.
Schema	

1.0 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

1.1 Specific Aims and Hypothesis

1.1.1 Hypothesis

Malignant gliomas are the most common primary brain tumors in adults [1]. The standard of care for newly diagnosed high grade glioma, especially glioblastoma multiforme (GBM), is maximal surgical resection, followed by radiation treatment (RT) and concurrent and adjuvant chemotherapy with temozolamide (TMZ) [2]. Nonetheless, 90% of the patients recur within 2 years [2, 3]. There is no standard treatment for recurrent high grade glioma. Therapeutic options include repeat surgery, re-irradiation, cytotoxic agents, and target therapies. Fractionated stereotactic radiotherapy (FSRT) may offer some improvement in survival with minimal toxicity for patients with previously treated gliomas. Our institution published one of the largest single institution experiences of using FSRT in recurrent high grade glioma. The treatment is well tolerated with a favorable median survival of 11 months after FSRT. Aurora kinase A is overexpressed in many malignant tumors [4]. Overexpression of Aurora-A has a prognostic value in high grade glioma. Administration of Aurora-A kinase inhibitor can suppress the growth of GBM, as well as be synergistic to radiation treatment [5-8]. Alisertib (MLN8237) is a potent second generation Aurora-A kinase inhibitor [4, 9, 10]. Combining FSRT with Alisertib for patients with recurrent high glioma likely would result in improved local control and prolonged survival. The effect of combination therapy may be more than additive effect, as suggested by a preclinical study [7]. The current phase I study will assess the safety profile of combining different doses of Alisertib with FSRT. We will determine the MTD (maximum tolerated dose), as well as a recommended phase II trial dose of Alisertib when used concurrently with radiation treatment for recurrent glioma patients.

1.1.2 Primary Aims:

- Evaluate the safety and tolerability of the study treatment
- To determine the Maximum Tolerated Dose (MTD) of Alisertib when combined with fractionated stereotactic radiation treatment for recurrent high grade glioma.

1.1.3 Secondary Aims:

- To estimate 6 month progression free survival rate
- To estimate the median time to progression
- To estimate overall survival
- To estimate the impact on quality of life (QoL)

1.2 Background and Rationale

1.2.1 Recurrent glioma

High-grade gliomas are the most frequent primary brain tumor seen in adults. The addition of temozolomide (concurrent and adjuvant) to radiation therapy in the upfront setting improved overall survival in a phase III trial from 12.1 to 14.6 months [2, 3]. Nonetheless, following radiation therapy, 90% of gliomas recur within 2 years. The aggressive nature of gliomas is

explained in terms of inappropriate activation of pro-survival pathways (esp. PI3 Kinase) [11, 12], aberrant DNA repair [13], prominent angiogenesis [14], and multiple aberrations in the epigenetic control of gene expression [15].

Gliomas frequently recur close to their site of origin, making re-treatment challenging; furthermore, gliomas become more aggressive over time [16-18]. Continued tumor growth produces neurological symptoms and eventual death. Poor prognostic factors include increased age, lower Karnofsky performance score (KPS), initial and on-study histologies of glioblastoma multiforme (GBM), corticosteroid use, shorter time from original diagnosis to recurrence, and tumor outside frontal lobe [19]. Overall survival for relapsed glioma is less than 8 months.

There is no standard treatment for recurrent tumor; therapeutic options include repeat surgery [20-22], re-irradiation [23-29], cytotoxic agents [30-32] and anti-angiogenic therapy [33-37]. Bevacizumab is an FDA approved agent for recurrent glioma that produces a response rate of 30-40% and a median overall survival of 9 months [38]. Unfortunately, there is emerging evidence that tumors that progress on bevacizumab are extremely resistant to other therapies as well [39], suggesting that bevacizumab may be best reserved for after other modalities have been exhausted.

1.2.2 Fractionated Stereotactic Radiation Therapy (FRST)

Radiation therapy is thought to kill living cells through the induction of DNA damage, in particular DNA double strand breaks. Due to a variety of practical and technical reasons, normal tissue is often incorporated into the 'target volume'. Early radiotherapists discovered that fractionating the treatment (i.e. delivering it in many small daily doses over a number of weeks) is a way of damaging tumor tissue more than normal tissues. In stereotactic radiosurgery (SRS) on the other hand, a large dose of radiation is delivered in a single session to a stereotactically defined intracranial volume. SRS avoids toxicity by its high degree of precision in target definition, thus avoiding radiating normal structures.

Fractionated stereotactic radiotherapy combines the precision of stereotactic positioning with the radiobiologic advantage of fractionation. FSRT, as utilized in this trial, utilizes a frameless mask system with daily stereotactic images for precise localization. FSRT is delivered by a Novalis LINAC based teletherapy unit.

The Jefferson FSRT program is headed by Dr. David Andrews, a pioneer in the field. Neurosurgeons, Radiation oncologists and neuro-oncologists work closely together to obtain consensus treatment decisions. Following the acquisition of CT and contrast enhanced MRI images (obtained with face mask in place) treatment is planned by a dedicated team of physicists and therapists.

Early Jefferson experience determined that re-irradiation with FSRT was extremely well tolerated in recurrent glioma; there were no ≥ grade 3 toxicities in 20 patients [23]. Gross tumor volume (GTV) was defined by the gadolinium-enhanced tumor edge using T1 weighted series. The PTV was considered equivalent to the GTV and edema was not included in the treatment volume. Tumors were treated to the 85-90% isodose line and coverage of the target volume was reviewed on the planning system.

A report on 147 patients with recurrent high grade gliomas (Grade 3 astroctoma or GBM) undergoing this treatment between 1994 and 2008 was recently published in the Journal of Clinical Oncology [29]. The median age at primary diagnosis was 53 years (range, 19 to 86 years). Sixty-seven patients (45%) were female. At initial diagnosis, 105 patients (71%) were diagnosed with GBM and 42 were diagnosed with anaplastic astrocytoma. All patients received initial postoperative conformal fractionated RT to a mean and median dose of 60.0 Gy in daily 2.0 Gy fractions. Eighty-four patients (60%) had surgical resection of their progressive glioma prior to salvage FSRT. Forty-eight of the 147 patients received various chemotherapy agents (mostly temozolomide) at recurrence together with FSRT.

Toxicity was minimal; no patients demonstrated clinically significant acute morbidity and all patients were able to complete the prescribed radiation dose without interruption. No patient required hospitalization or surgery for early acute or delayed toxicity.

The median time from diagnosis to H-SRT was 8 months (range 4-205 mo). Median survival time from the start of FSRT was 10 months (8, 12 mo) for patients with grade 3 tumors and 11 months (9, 14) in grade 4 patients. Three month follow up MRI scans following H-SRT indicated stable disease in 89 (60%). Minimal response as defined by Macdonald criteria was noted in 15 (10%) patients and progression was noted in 43 (30%) patients.

The University of Heidelberg has published their experience of re-irradiation for recurrent gliomas in 172 patients. Fractionated stereotactic radiation therapy was performed with a median dose of 36 Gy in 2 Gy fractions. This regimen was well tolerated and resulted in modest survival (survival from re-irradiation for grade 3 and 4 patients was 16 months and 8 months respectively). The largest series of re-irradiation of recurrent gliomas examined 172 patients with recurrent gliomas of which 111 had high-grade gliomas [24]. Fractionated stereotactic radiation therapy was performed with a median dose of 36 Gy in 2 Gy fractions. This regimen was well tolerated and resulted in modest survival. Similar to our study age and extent of initial neurosurgical resection at diagnosis influenced survival and no relationship was found between time to progression and survival benefit from re-treatment. In contrast to our results, no relationship between volume at re-irradiation and post re-irradiation survival was identified. The role of second resection, chemotherapy with re-irradiation and influence of dose were not reported. Of note, survival from re-irradiation for grade 3 and 4 patients was 16 months and 8 months respectively compared to 10 months and 11 months in our series. These differences are likely attributable to differences in patient populations, most notably age (median age was 41 versus 53 in this report).

The best reported survival for standard fractionated re-irradiation combined with chemotherapy was reported by an Italian group [40]. Thirty-one patients received external beam RT to a dose of 34.5 Gy with concurrent lumustine (CCNU) and reported a 13.5-month MST after re-irradiation. Other studies combining re-irradiation with chemotherapy have demonstrated similar results [24, 40, 41].

1.2.3 Aurora A Kinases and the Aurura A Kinase Inhibitor Alisertib (MLN8237)

Alisertib is a selective small molecule inhibitor of Aurora A kinase that is being developed for the treatment of advanced malignancies. Aurora A kinase belongs to a highly conserved family

of serine/threonine protein kinases that also includes Aurora B and Aurora C. Aurora A and Aurora B are expressed in all actively dividing cells, while Aurora C expression is largely restricted to dividing germ cells [42]. Aurora A localizes to centrosomes and the proximal mitotic spindle during mitosis where it functions in a diverse set of mitotic processes.

The evidence supporting Aurora A kinase as a therapeutic target for the treatment of malignancies comes from several sources. First, the Aurora A kinase gene is amplified and/or overexpressed in many tumors, including colon, breast, pancreatic, and bladder cancers, as well as certain lymphomas, leukemias, and myeloma [43-47]. Aurora A overexpression in human cancers has been correlated with increased aneuploidy and centrosome amplification [48]. Second, forced overexpression of Aurora A kinase in experimental models results in the transformation of normal cells, suggesting that Aurora A overexpression may be oncogenic [43]. Lastly, in a number of different experimental systems, Aurora A inhibition leads to mitotic delays and severe chromosome alignment and segregation defects, followed by cell death [49-52]. Overall, the essential role of Aurora A in mitotic progression and its dysregulation in certain cancers makes it an attractive therapeutic target.

Given the obligatory role of mitosis in tumor proliferation, an Aurora A inhibitor would be expected to have potential applications across a broad range of human tumors, including GBM. Indeed, MLN8237 has demonstrated activity against a variety of nonclinical solid tumor and hematological malignancy models grown in vitro and in vivo [53, 54].

1.2.4 Rationale

Aurora A is expressed in many types of cancer in which polyploid cells containing multiple centrosomes are observed. Aurora-A localizes to the centrosomes, where it is required for their maturation and separation, thereby promoting mitotic entry and spindle assembly. In mitosis, Aurora-A associates with the spindle poles and is involved in both centrosomal assembly and acentrosomal spindle assembly. The gene encoding Aurora-A lies within a region of chromosome 20q13, which is amplified in many epithelial malignant tumors, including breast, gastric, colon, ovarian, glioma and pancreatic cancers. Furthermore, overexpression of an active mutant of Aurora-A in rat1 cells induced neoplastic transformation, indicating that Aurora-A is an oncogene. Overexpression of Aurora-A contributes to genetic instability and tumorigenesis by disrupting the proper assembly of the mitotic checkpoint complex. In addition, this kinase is a key regulatory component of the p53 pathway and its overexpression leads to an increase in p53 degradation, which again facilitates oncogenic transformation. Overexpression of aurora kinase appears to have prognostic value in high grade glioma. Administration of aurora kinase inhibitor can suppress the growth of glioblastoma model [8]. Moreover, inhibition of aurora-A kinase is found to synergize with radiation in glioblastoma cells [55, 56]. Alisertib (MLN8237) is a second generation AURKA inhibitor and has recently entered phase I/II clinical trials. Early clinical studies showed promising result against multiple types of cancers when used alone. Combining Alisertib with FSRT in patients with recurrent GBM likely would result in enhanced therapeutic effects. The current phase I study will assess the safety profile of combining different doses of Alisertib with standard dose FSRT in patients with recurrent GBM. We will determine the MTD (maximum tolerated dose), as well as a recommended phase II trial dose of Alisertib.

1.3 Study Therapy

1.3.1 FSRT

Fractionated stereotactic surgery (FSRT) will be administered once daily, every weekday for a total of 10 daily treatments. All subjects will receive the 30-35 Gy in 10 daily fractions, as determined by the treating physician. Radiation treatment interruptions for up to 3 days are permitted for any reason. Interruptions of 4 to 7 treatment days will be considered an acceptable protocol violation. For interruptions of 8 days or greater, an unacceptable deviation will be assigned.

All patients will have CT simulation and high resolution MRI with contrast for radiation treatment planning. The gross tumor volume (GTV) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This will generally include the surgical cavity margins from the most recent surgical procedure as well. There is no clinical target volume (CTV) or planned target volume (PTV) expansion.

All patients will receive 35 Gy in 3.5 Gy fractions. This dose maybe reduced to 30 Gy in 10 fractions per the treating physician if the GTV is large (> 50 cc) or close to critical structures (such as brainstem, optic nerves, or chiasm). The dose is prescribed to the highest isodose line that covers >99% of the GTV.

1.3.2 Alisertib treatment

Alisertib will be administered by mouth, twice daily on days of radiation treatment during the course of FSRT. All patients will receive 10 days of Alisertib, concurrent with 10 daily radiation treatments. The first dose should be administered on the day of, but prior to, the first radiation treatment. The dose of Alisertib will be determined according to the protocol.

During the maintenance therapy period, Alisertib will be administered by mouth, at 50 mg twice daily from day 1 to day 7 of a 21-day cycle. All patients will receive up to 18 cycles, or until tumor progression.

1.4 Preclinical Data

1.4.1 In Vitro Studies

Alisertib is an adenosine triphosphate (ATP)-competitive and reversible inhibitor of Aurora A kinase in vitro with an inhibition constant (Ki) of 0.43 nM. In cultured HCT-116 human colorectal tumor cells, Alisertib produces 50% inhibition of Aurora A kinase activity at a concentration of 6.7 nM. It is approximately 200-fold more selective for Aurora A kinase than the structurally related family member, Aurora B kinase (half maximal inhibitory concentration [IC50] = 1534 nM). Moreover, in enzyme assays, Alisertib is selective for Aurora A kinase when compared to other kinases and receptors. Alisertib has affinity for the gamma acid alpha 1 (GABAA α1) receptor benzodiazepine (BZD) binding site (Ki = 290 nM). The consequences of GABAA binding in rat and dog safety pharmacology studies are discussed below.

Consistent with the mechanism of action for an Aurora A kinase inhibitor, Alisertib treatment results in formation of abnormal mitotic spindles, an accumulation of mitotic cells, and a decrease in the proliferation of a broad range of tumor cell lines grown in culture [49, 57, 58].

The in vitro antiproliferative effect of Alisertib was quantified in tumor cell lines derived from a variety of malignancies, including colon (3 cell lines), breast (1 cell line), lung (1), ovary (1), prostate (1), pancreas (1), and lymphoid (1). Alisertib inhibited proliferation with lethal concentrations for 50% cell-growth inhibitor concentrations (GI50 values) ranging from 16 to 469 nM, demonstrating that Alisertib is a potent inhibitor of proliferation in diverse human tumor cell lines.

1.4.2 In Vivo Studies

Alisertib has demonstrated broad antitumor activity in a diverse array of experimental human tumor xenografts when dosed QD or BID. These include 2 colon models (HCT-116 and DLD-1), 2 lung models (H460 and Calu-6), 1 breast model (MDA-MB-231 FP4), 1 prostate model (CWR22 RV-1 Luc1.17) and 4 DLBCL models (Ly19, WSU, Ly7, PHTX 22-06). Statistically significant tumor growth inhibition (TGI) was observed with Alisertib given at 30 mg/kg QD or less in all models but the Calu-6 model. At 20 mg/kg BID or less, statistically significant TGI was observed in all models tested, including Calu-6. Taken together, these results demonstrated that Alisertib has broad antitumor activity in many experimental human tumor models.

Alisertib also demonstrated robust antitumor activity when combined with docetaxel in preclinical models. Alisertib dosed daily at 3, 10 or 20 mg/kg QD was tested with docetaxel dosed weekly at 5 or 10 mg/kg in mice bearing breast (MDA-MB-231), primary breast (PHTX-02), lung (H522) or prostate (CWR22 RV-1 Luc1.17) human tumor xenografts. The various combinations of these agents at these doses were well tolerated, and resulted in synergistic or additive antitumor activity relative to the single agent activity of either Alisertib or docetaxel alone. In several of these models, the combination of Alisertib and docetaxel led to regression in tumor size and a dramatic prolongation in survival after termination of treatment. When the taxane was delivered in a regimen that overlapped Alisertib exposure during the first week of dosing, major enhanced antitumor activity was observed when Alisertib was administered over a shorter (9-day) time period, and the magnitude of response and disease control was comparable to results obtained with a longer (21-day) dosing schedule. In the prostate cancer model (CWR22 RV1), the combination Alisertib (10 mg/kg QD) and docetaxel (10 mg/kg Q7D x 3) led to regression in tumor size and a dramatic prolongation in overall survival after termination of treatment.

Clinical pharmacokinetic data available as of 20 April 2012 are summarized in Section 5.2 of the IB. Upon oral administration of PIC formulation to patients with advanced nonhematologic malignancies, absorption of Alisertib was fast, with peak plasma concentrations generally achieved by 2 hours post-dose. Negligible urinary excretion of Alisertib was observed in humans. The renal clearance of Alisertib in humans was less than 0.1% of apparent oral clearance. Steady-state plasma exposures of Alisertib increased in an approximately dose-proportional manner over the range of 5 to 200 mg/day in patients with advanced solid tumors. Overall mean steady-state terminal half-life following multiple-dose administration in patients with nonhematologic malignancies was approximately 22 hours. The overall mean peak/trough ratios were 2.6 and 5.0 for BID and QD dosing, respectively. The overall mean accumulation ratios were 2.8 and 1.9 for BID and QD dosing, respectively. Pharmacokinetic steady-state conditions were approximately achieved by Day 7 following daily oral administration.

Based on the results of a population PK analysis in 294 adult cancer patients, the apparent oral clearance of MLN8237 CL/F was unaffected by age, body weight, BSA, or the UGT1A1 genotype (number of *28 alleles). These results support the use of a common fixed starting dose of MLN8237 independent of UGT1A1 genotype status, age or body size in the adult patient population, in the ongoing and planned clinical trials.

Results from the relative BA study in 14 patients indicated that systemic exposures achieved following administration of the enteric-coated-tablet (ECT) and powder-in-capsule (PIC) formulations of MLN8237 are generally similar, based on relative BA of ECT in reference to PIC of approximately 90% (90% confidence interval: 74.4%-108.8%), supporting transition from the PIC to ECT in clinical development.

The absolute bioavailability of Alisertib in humans has not been determined; however, the single-dose pharmacokinetics of a prototype oral solution formulation of Alisertib (25-mg dose) were characterized in reference to the PIC (50-mg dose) in a cross-over relative bioavailability evaluation in Study C14010 in 15 patients with nonhematologic malignancies. Following administration as an oral solution, Alisertib was rapidly absorbed, with a median Tmax of 1 hour. Based on preliminary PK data, the dose-normalized geometric mean of Alisertib Cmax and AUCinf achieved following administration of the oral solution were approximately 78% and 35% higher, respectively, than those observed following PIC dosing.

The effect of a standardized high-fat meal on the PK of single dose Alisertib administered as a 50-mg strength ECT formulation was evaluated in 14 patients with advanced solid tumors. The lack of an effect of food on Alisertib AUCinf observed in this study supports the conclusion of the lack of a clinically meaningful effect of food on the PK of Alisertib ECT. The results of this study, therefore, support a recommendation that Alisertib may be dosed without regard to the timing of meals in future clinical studies employing the ECT formulation, unless otherwise specified in the clinical study protocol.

1.5 Clinical Data to Date

Clinical experience with Alisertib includes phase 1 and 2 studies in both solid tumors and heme-lymphatic malignancies, described below.

Alisertib for clinical studies is being developed in 3 dosage formulations: powder-in-capsule (PIC), enteric-coated-tablet (ECT), and oral solution (OS: for pediatric use). The initial studies employed the PIC formulation, and more recent studies have evaluated safety, PK, relative bioavailability (in reference to the PIC), and antitumor activity after administration of the ECT formulation.

Using the ECT formulation, the dose-escalation, phase 1 portion of an ongoing study, C14007, has evaluated multiple dose levels from 10 to 60 mg BID for 7 days in repeat, 21-day cycles and 50 mg BID has been determined to be the MTD.

In Study C14007, which includes a phase 1 dose escalation using the same ECT formulation employed in this study, multiple dose levels up to 840 mg total cycle dose (60 mg BID for 7 days) were evaluated. At the maximum administered dose of 60 mg BID for 7 days

administered to patients with advanced solid tumors, 3 patients (out of 3 enrolled) developed myelosuppression during the treatment-free period which was considered intolerable and above the MTD of 50 mg BID. In summary, 700 mg total cycle dose (e.g., 50 mg BID administered daily for 7 days) represents the ceiling for dose escalation in these combinations with Alisertib planned for this current study.

The predominant toxicities reflect the mechanism of action in proliferating tissue (bone marrow, GI epithelium, and hair follicles). The suggested management of these toxicities is based on standard clinical paradigms for an anti-proliferative chemotherapeutic agent. Using a treatment-free period for recovery between each cycle of drug administration, the clinical experience from multiple phase 1 through 2 studies indicate that major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 12 months.

Alisertib is structurally related to the benzodiazepines (BZD) (e.g., diazepam, lorazepam) and also has activity against the GABAAα1 BZD receptor. BZD-like effects (e.g., somnolence, confusion, memory loss) have been observed to be associated with the onset of maximal plasma concentration (e.g., Tmax [time to maximum plasma concentration]). CNS effects associated with peak plasma levels have been generally managed by administration of divided doses (e.g., BID administration), although dose reductions have sometimes been required. While CNS effects attributed to Alisertib were also generally reversible and manageable by dose delay or reduction, the causal relationship, and thus optimal approach to management, were sometimes confounded by diverse causes including, but not limited to, concomitant medications (e.g., narcotic analgesics, antianxiety medications), comorbidities (e.g., infection, anemia, electrolyte abnormalities), and progressive malignancy (e.g., brain metastases).

1.6 Dose Rationale and Risk/Benefits

The safety risks of Alisertib treatment are: (1) leukopenia, neutropenia, febrile neutropenia, and lymphopenia with a potential increased susceptibility to infection; (2) thrombocytopenia with a potential increased risk of bleeding; (3) anemia; (4) gastrointestinal (GI) toxicity resulting in stomatitis/mucositis, nausea, vomiting, anorexia, abdominal pain, dyspepsia, diarrhea, dehydration, and potentially mucosal/GI bleeding, and sepsis; (5) alopecia; (6) asthenia/fatigue; (7) fever; and (8) benzodiazepine-like effects including sedation, somnolence, sleep disorders, confusion, disorientation and associated memory loss and gait disturbances (which were reversible in clinical studies with cessation of treatment or dose reduction). Skin changes including hand-foot syndrome have been reported in some patients. Clinical safety data includes experience from patients who received multiple cycles followed by treatment-free periods between each cycle, and from patients who reduced or discontinued treatment. Based on the available clinical data, drug abuse, dependency, and withdrawal were not observed.

While these toxicities are potentially associated with risk or discomfort to the patient, they are anticipated to be reversible. Alisertib has not led to major neurotoxicities or fluid retention as a single agent. However, because there is only limited human experience with Alisertib, it is possible that Alisertib will have other toxicities that have not been observed in, or predicted based on, rat, dog, and human studies. Alisertib has a low potential to prolong the QT interval in vivo based upon its extremely weak in vitro binding to hERG (IC50 and Ki both > 100 μM).

To mitigate the inherent risks in clinical studies of Alisertib, patients are evaluated frequently while they are receiving treatment.

Because Alisertib inhibits Aurora A kinase, it is possible that Alisertib may interfere with cancer growth and cause cancer cell death through a potentially non-cross resistant pathway as compared to other agents that patients may have received. The clinical utility of these effects will be investigated in current and future studies.

2.0 Study Objective

2.1 Primary Objectives:

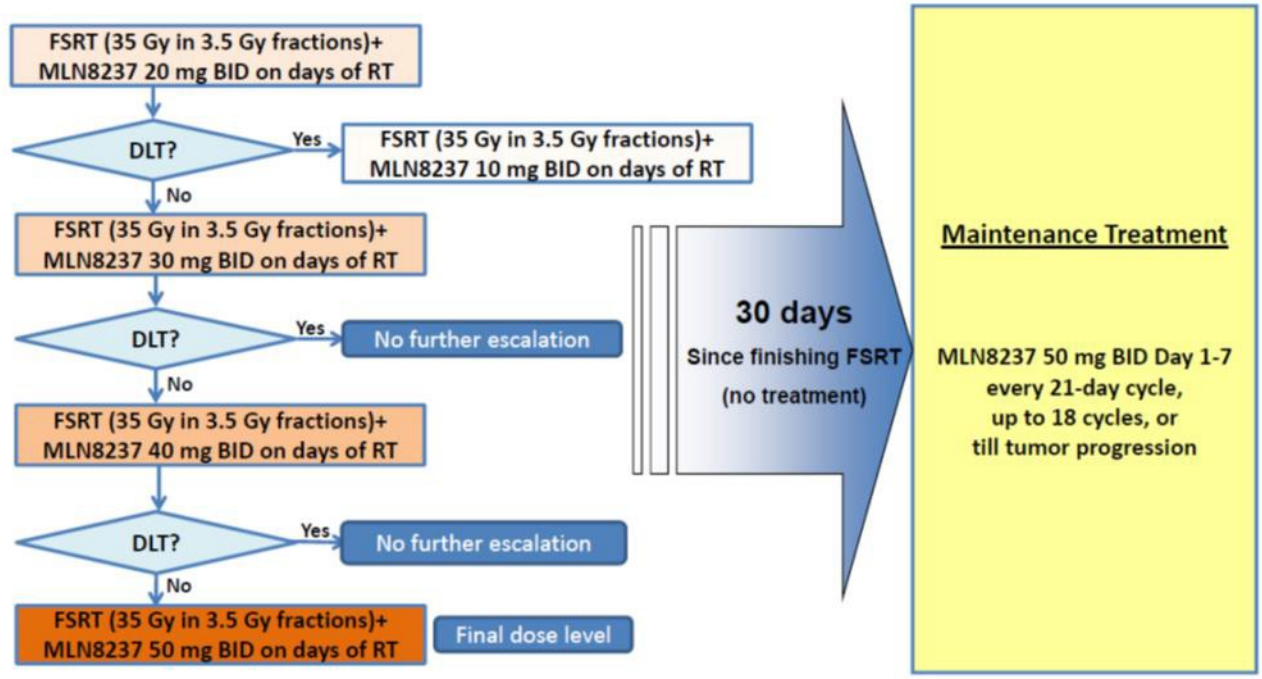
1. Evaluate the safety and tolerability of the study treatment
2. To determine the Maximum Tolerated Dose (MTD) of daily oral ALISERTIB when combined with fractionated stereotactic radiation treatment for recurrent high grade glioma.

2.2 Secondary Objectives:

1. To estimate 6 month progression free survival rate
2. To estimate the medial time to progression
3. To estimate overall survival
4. To estimate the impact of quality of life (QoL)

3.0 STUDY DESIGN

3.1 General Design



3.2 Primary Study Endpoints

1. Evaluate the safety and tolerability of the study treatment
2. To determine the Maximum Tolerated Dose (MTD) of daily oral ALISERTIB when

combined with fractionated stereotactic radiation treatment for recurrent high grade glioma.

3.3 Secondary Study Endpoints

1. To estimate 6 month progression free survival rate
2. To estimate the medial time to progression
3. To estimate overall survival
4. To estimate the impact of quality of life (QoL)

3.4 Primary Safety Endpoints

To determine the Maximum Tolerated Dose (MTD) of daily oral ALISERTIB when combined with fractionated stereotactic radiation treatment for recurrent high grade glioma.

4.0 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

1. Patients must have a previously histologically or cytologically confirmed high grade glioma (astrocytic or oligodendroglial supratentorial tumors grade 3 or 4) that has been previously treated with fractionated radiation therapy and now shows evidence of recurrence.
2. Patients must have recovered from the toxic effects of prior therapy.
3. Patients must have recovered from the effects of surgery. There must be a minimum of 21 days from the day of surgery to the day of protocol treatment. For core or needle biopsy, a minimum of 7 days must have elapsed prior to the day of protocol treatment.
4. Prior treatment with cytotoxic and biological agents is permissible. There should be at least a 2-week break between prior treatment and the protocol treatment.
5. Prior treatment with fractionated radiation therapy (up to 60Gy) is an eligibility criterion, however there should not have been a second course of fractionated radiotherapy to the supratentorial area.
6. One prior single fraction radiosurgical procedure within the treatment field is acceptable if V12<5 cc (V12 is the volume of normal brain (outside GTV) receiving 12 or more Gy). Additional radiosurgical procedures outside of the treatment area are acceptable.
7. Subject must be able to take oral medication and to maintain a fast, is required for 2 hours before and 1 hour after MLN8237 administration.
8. ANC > 1500/mm^3, platelets > 100,000/mm^3, Hgb > 9 g/dL. Values must be obtained without need for myeloid growth factor or platelet transfusion support within 14 days of registration. However, erythrocyte growth factor is allowed as per published ASCO guidelines.
9. Total bilirubin ≤ ULN, SGOT (AST) and SGPT (ALT)< 1.5 x ULN, within 14 days of registration.
10. Adequate renal function as defined by: calculated creatinine clearance must be ≥40 mL/minute (Cockcroft-Gault), within 14 days of registration.
11. Age >18 years.
12. ECOG performance status <2 (see Appendix I).
13. Life expectancy of greater than 2 months.
14. Women of childbearing potential must have a negative β-HCG pregnancy test documented within 7 days prior to registration.

15. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for 4 months after last dose.
16. Ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

1. Known history of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness such as severe chronic obstructive pulmonary disease requiring supplemental oxygen.
2. Systemic infection requiring IV antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.
3. Myocardial infarction within 6 months prior to enrollment, New York Heart Association (NYHA) Class III or IV heart failure, 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.
4. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum □-human chorionic gonadotropin (□-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
5. Patient has received other investigational drugs within 14 days before enrollment
6. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
7. Other severe acute or chronic medical or psychiatric condition, including uncontrolled diabetes, malabsorption, resection of the pancreas or upper small bowel, requirement for pancreatic enzymes, any condition that would modify small bowel absorption of oral medications, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for enrollment in this study.
8. Treatment with clinically significant enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine or phenobarbital, or rifampin, rifabutin, rifapentine or St. John's wort within 14 days prior to the first dose of MLN8237 and during the study.
9. Known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C. Testing is not required in the absence of clinical findings or suspicion.
10. Patients have a history of any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated basal or squamous cell carcinoma of skin, superficial bladder cancer or carcinoma in situ of cervix, AJCC (version 7.0) stage 0 or I breast cancer, AJCC (version 7.0) stage I, or II prostate cancer.
11. Radiation therapy to more than 25% of the bone marrow. Whole pelvic radiation is considered to be over 25%.
12. Patients who cannot swallow whole tablets (i.e. medication tablets)

4.3 Gender/Minority/Pediatric Inclusion for Research

This study includes both genders and minority patients. Pediatric patients are excluded.

4.4 Subject Recruitment and Screening

Patients who are 18 years of age or older with high grade gliomas are eligible for the study. Patients can be recruited from PI or co-investigators' clinical practices. Principal Investigator and research nurses/research associates should be notified of potential study subjects. Appropriate laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria will be ordered through the recruiting physician. PI of the study or study designated research nurse/research associate will screen and determine the final eligibility of the subject for enrollment.

4.5 Early Withdrawal of Subjects

4.5.1 When and How to Withdraw Subject

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:

1. Intercurrent illness
2. Occurrence of an unacceptable adverse event
3. A treatment delay >3 weeks
4. Patient request
5. Protocol violations based on the judgment of PI
6. Non-compliance
7. Administrative reasons
8. Failure to return for follow-up
9. General or specific changes in the patient's condition that make it unacceptable to continue treatment, in the judgment of the investigator
10. Progressive disease

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

4.5.2 Data Collection and Follow-Up for Withdrawn Subjects

According to FDA regulations, when a subject withdraws from the study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

A subject who discontinues study treatment needs to state whether he/she wishes to continue participating in the study and allow further data collection as part of long term follow-up. Subjects who choose to continue with the study will participate in follow-up visits and evaluations according to the protocol. Subjects who refuse to participate in follow-up will be withdrawn from the study.

Study data collected prior to a subject's withdrawal from the study will be included in the study analysis.

5.0 Study Drug

5.1 Description

Alisertib is supplied as the ECT dosage form in 10 mg strength, with dose strength expressed as the milligrams of active drug (free acid).

5.2 Treatment Regimen

Alisertib will be administered by mouth, twice daily on days of radiation treatment during the course of FSRT. All patients will receive 10 days of Alisertib, concurrent with 10 daily radiation treatments. The first dose should be administered on the day of, but prior to, the first radiation treatment. The dose of Alisertib will be determined according to the protocol.

During the maintenance therapy period, Alisertib will be administered by mouth, at 50 mg twice daily from day 1 to day 7 of a 21-day cycle. All patients will receive up to 18 cycles, or until tumor progression

5.3 Risks

Most Common (≥ 30%)

- Nausea, diarrhea
- Decreased number of white blood cells, which may increase risk of infection
- Damaged mucous membranes in the mouth (mouth blisters)
- Decreased number of red blood cells (or anemia) which may cause feelings of tiredness
- Weakness or feeling tired
- Hair loss

Very Common (10% and <30%)

- Pain, including muscle pain, chest pain, and pain from cancer
- Fever with or without decreased white blood cells
- Sleepiness or feeling drowsy
- Bleeding events with or without decreased number of blood platelets
- Cough
- Shortness of breath
- Rash/skin eruption
- Constipation
- Vomiting
- Decrease in weight or loss of appetite
- Fluid retention and swelling (e.g., hands, feet, legs)
- Headache
- Dehydration (decreased body fluids)
- Dizziness

Common (>1% and <10%)

- Confusion and mental status changes
- Imbalance which can lead to falling
- Anxiety or depression
- Difficulty sleeping

- High or low blood pressure
- Itchy or dry skin
- Bruises
- Inflamed or dry eyes, blurred vision
- Dry mouth
- Difficulty or painful when swallowing, altered taste
- Upset stomach, flatulence
- Difficult or blocked bowel movements
- Hemorrhoids
- Runny nose, sinus or voice problems
- Numbness or tingling in hands or feet
- Abnormal heart rhythm
- Ringing in the ears
- Muscle spasms/weakness
- Fluid around the lungs or abdomen
- Increased sweating or chills
- Abnormal kidney function
- Abnormal liver function test
- Abnormal levels of blood sugar, chemistry, protein or blood clotting time
- Bacterial, fungal or viral infection
- Increased blood bilirubin
- Blood clot (usually in the legs)
- Loss of bladder control

Uncommon (< 1%)
Serious and treatment-related adverse events include: rhabdomyolysis (muscle breakdown that can damage kidneys), bone fracture, blistering skin reaction, multiple organ failure, deafness, shock, hepatic veno-occlusive disease (also known as sinusoidal obstruction syndrome), heart problems, agitation or irritability, and injury to one or more organs that may be life-threatening or fatal.

5.4 Method of Assigning Subjects to Treatment Groups
This is an open label phase I study.

5.5 Preparation and Administration of Study Drug
Alisertib will be administered on an empty stomach with the patient remaining NPO (nothing by mouth), except for water and prescribed medications, for 2 hours before and 1 hour after each dose. Patients will be instructed to take each oral dose of Alisertib with 8 ounces (1 cup, 240 mL) of water.

Alisertib will be supplied as 10 mg ECT, with the dose strength expressed as milligrams of active drug (free acid). All tablets are to be ingested whole; patients who have difficulty swallowing tablets will be excluded from the study.

5.6 Subject Compliance Monitoring
Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. The radiation treatment record will be reviewed and recorded.

5.7 Prior and Concomitant Therapy
Anti-emetogenic agents may be administered at the discretion of the investigator. Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is discouraged because of the potential benzodiazepine-like effects of Alisertib.

Other medications, such as PPIs, H2 antagonists, growth factors, glucocorticoids, anti-emetics, and anti-epileptics are permitted at the treating physician's discretion.

All patients will receive concurrent FSRT to the recurrent glioma.

5.8 Packaging
Alisertib will be supplied as 10 mg ECT, with the dose strength expressed as milligrams of active drug (free acid).

5.9 Blinding of Study Drug

5.10 Receiving, Storage, Dispensing, and Return
5.10.1 Receipt of Drug Supplies
Millennium will provide Alisertib.

Upon receipt of the study treatment supplies, an inventory must be performed and a drug receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must notify study sponsor of any damaged or unusable study treatments that were supplied to the investigator's site.

5.10.2 Storage
Alisertib must be stored in a secure area according to local regulations.

The investigator must ensure that it is stored in accordance with the environmental conditions as determined by Millennium and defined in the Investigator Brochure or SmPC/reference label. Alisertib must be stored at room temperature.

5.10.3 Dispensing of Study Drug
It is the responsibility of the investigator to ensure that Alisertib is only dispensed to study subjects. The Alisertib must be dispensed only from official study site by authorized personnel according to local regulations.

5.10.4 Return or Destruction of Study Drug
It is the responsibility of the investigator to ensure that a current record of Alisertib disposition is maintained at each study site where Alisertib is inventoried and disposed of. Records or logs

must comply with applicable regulations and guidelines and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number and use date or expiry date.
- Non-study disposition (e.g., lost, wasted, broken).

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6.0 STUDY PROCEDURES

6.1 Study Visit Schedule

Please see ***Appendix II*** for study calendar.

6.2 Definition of Dose-Limiting Toxicities

Dose-limiting toxicities (DLTs) will be graded in severity according to the guidelines outlined in the NCI- CTCAE version 4.0. Dose-limiting hematologic and non-hematologic toxicities will be defined differently, and will be based on events that occur during study drug administration and for 30 days after the completion of the radiation therapy. In order to be declared a dose-limiting toxicity, an adverse experience must be related (definitely, probably, or possibly) to study therapy.

If a patient experiences a DLT during the radiation phase or the 30 day post radiation observation period, the patient will be permanently discontinued from study.

A dose-limiting toxicity (DLT) will be defined as follows:

- All grade 3 or higher toxicities that occur during or within 30 days of completing radiation treatment will be considered "treatment related" with the exception of (1) symptoms that are clearly related to the cancer or other pathology (in the opinion of the treating physician), and (2) expected sequelae of the neurosurgical procedure or radiosurgery. All neurological symptoms will be considered "treatment related" unless they are present at study onset, expected sequelae of the neurosurgical procedure, or clearly related to disease progression.
- Febrile neutropenia (even in the absence of hospitalization)
- Hematologic DLTs will be defined as either Grade 4 neutropenia lasting for $\geq$ 7 days in duration, any Grade 4 anemia, any Grade 4 thrombocytopenia, or any Grade 5 hematologic toxicity. All patients will be evaluated for hematologic toxicity.
- Any neurological toxicity of Grade 3, 4 or 5 will be considered a DLT, with the exception of 1) symptoms present prior to study enrollment, and 2) expected sequelae of the neurosurgical procedure.
- Grade 3 event of hypocalcemia, hypophosphatemia, hypokalemia, or hypomagnesemia lasting more than 24 hours without responding to medical therapy; or responding to medical therapy and lasting more than 72 hours
- Grade 3 transaminases elevation associated with $\geq$ grade 2 bilirubin elevation (Hy's law)

will also be a DLT defining event.

- Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4 or 5 non-hematologic toxicity, with the specific exception of:
    - Grade 3 nausea or Grade 3 vomiting that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
    - Grade 3 diarrhea that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
    - Grade 3 dehydration that, in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures and lasts for less than 48 hours.
    - Grade 3 acidosis or alkalosis which responds to medical intervention by returning to ≤ Grade 2 within 48 hours.
    - Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 14 days in duration.
    - Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hyphosphatemia which responds to medical intervention.
    - Grade 3 hypercholesterolemia.
    - Grade 3 hypertriglyceridemia.
    - Grade 3 alopecia

6.3 Dose escalation/de-escalation

Dose escalation will proceed within each cohort according to a "3+3 design", as explained in the following scheme. Dose-limiting toxicity (DLT) is defined above. The toxicity assessment period is 30 days after the completion of the radiation therapy.

Dose Level	***Alisertib dose***
-1	*10 mg BID*
1	*20 mg BID*
2	*30 mg BID*
3	*40 mg BID*
4	*50 mg BID (final dose level)*

Number of Patients with DLT at a Given Dose Level[†]	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level.

	• If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.
†Dose escalation will be determined based on the occurrence of DLTs. For the purposes of determining whether to advance the Dose Level, DLTs will be counted by patient (i.e., a patient who experiences more than 1 DLT will be counted only once).	

6.4 Dose Delay and Dose Modification

If a patient experiences DLT during the radiation phase or 30 day post radiation observation period the patient will be permanently discontinued from the study.

Maintenance treatment with Alisertib will be repeated every 21 days. In order for a new cycle of therapy to begin, the patient's ANC must be ≥ 1,500/mm3 and the platelet count must be ≥ 75,000/mm3. In addition, any other toxicity considered by the investigator to be related to therapy with Alisertib must have resolved to ≤ Grade 1 or to the patient's baseline value before a new cycle of therapy may begin.

If the patient fails to meet the above-cited criteria for retreatment, then initiation of the next cycle of therapy will be delayed for up to 1 week. At the end of that week, the patient will be re-evaluated to determine whether the criteria for retreatment have been met. Should treatment need to be delayed for more than 1 week (i.e., a rest period of more than 21 days) because of incomplete recovery from treatment-related toxicity, the dose of Alisertib will be reduced 1 level when therapy resumes. A second dose reduction may occur should treatment need to be delayed for more than 1 week because of incomplete recovery from treatment-related toxicity on the reduced dosage. Should treatment need to be delayed for more than 2 weeks at any dose, therapy with Alisertib will be discontinued (Table 1).

Table 1 Table of Dose Adjustments for Maintenance Therapy

Dose Level	Dose	Schedule
1	50 mg	PO BID
-1	40 mg	PO BID
-2	30 mg	PO BID
-3	Discontinue	
Level 1 is the standard maintenance dose of 50 mg BID.		

Dose Modifications for Hematological Toxicity

If a patient experiences any of the following hematological toxicities during the dosing period, dosing will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment.

1. [redacted]
2. Grade 4 thrombocytopenia (platelet count < 25,000/μL) lasting more than 7 consecutive

days
3. Grade 3 neutropenia with fever or infection, or both, where fever is defined as an oral temperature greater than 38.5°C
4. Grade 3 thrombocytopenia with clinically significant bleeding

If a patient has a platelet count of less than 10,000/μl at any time, the patient will be removed from the study permanently.

Hematopoietic growth factors are allowed for febrile neutropenia or prolonged neutropenia, or decided appropriate by the treating physician. The choice of growth factor, dose, and duration is up to the treating physician. CBC should be monitored no less than 2 times a week till the toxicity is resolved to grade 3 or less.

Dose Modifications for Non-hematological Toxicities

If a patient experiences any of the following toxicities during the dosing period, dosing will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment, and treatment may resume after drug related toxicities have resolved to ≤ Grade 1 or to baseline.

1. Any Grade 2 or greater neurological toxicity
2. Any Grade 3 non-hematological toxicity that is considered by the investigator to be related to study drug other than:
3. Grade 3 arthralgias/ myalgias
4. Grade 3 or greater nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy (5-hydroxytryptamine 3 [5-HT3] serotonin receptor antagonist)
5. Grade 3 or greater diarrhea that occurs in the absence of optimal supportive therapy with loperamide
6. Grade 3 fatigue that lasts greater than 1 week
7. Grade 2 non-hematological toxicities that are considered by the investigator to be related to study drug and in the opinion of the investigator require dose reduction.

In general, Alisertib treatment should be discontinued if a patient experiences a nonhematologic grade 4 toxicity. If, in the opinion of the investigator and study sponsor it is in the patient's interest to continue therapy with Alisertib, then after recovery from the toxicity or toxicities in question to ≤ grade 1 or to baseline values, the dose of Alisertib should be reduced by at least 1 dose level with subsequent cycles of therapy.

When a dose reduction of Alisertib is required, no re-escalation of dose will be permitted. If a patient requires more than 2 dose reductions, therapy with Alisertib will be discontinued.

6.5 Quality of Life Measurement

The validated EORTC core quality of life questionnaire (QLQ-C30, version 3.0) supplemented by a brain cancer specific health-related quality of life questionnaire, QLQ-BN20, will be administered according to trial calendar. (Appendix V)

6.6 Define Progression

The progression of the glioma will be defined according to Updated Response Assessment

Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Work Group (RANO criteria) [59, 60].

7.0 STATISTICAL PLAN

7.1 Sample Size Determination

We use 3+3 design for this trial. We estimate up to 24 patients.

7.2 Statistical Methods

We will use a two-stage accrual design at each dose considered. We will initially enter 3 subjects at each dose. If none of the three experiences a dose-limiting toxicity we will proceed to the next dose. If one of the three experiences that level of toxicity, we will accrue 3 more subjects at that dose. If at any time there are two or more dose-limiting toxicities (in the 3-6 subjects) on a given dose, we will terminate accrual to the Phase I portion of that trial. No patient will be treated at a higher dose until the 3 or 6 patients have completed their toxicity evaluation period at the current dose. With this plan, a dose with a 50% or greater probability of causing a dose-limiting toxicity has at most a 12.5% chance of satisfying the conditions for dose escalation after the first 3 subjects and at least a 50% chance of stopping at 3. With the two-stages (3-6) together, there is at most a 17.2% chance of satisfying the conditions for dose escalation after the 6 subjects.

The maximally tolerated dose (MTD) will then be the last dose studied or the previous dose, based on Investigator's clinical judgment of the degree of toxicity seen at the last dose. While waiting for the 3 or 6 subjects accrued according to plan to complete their toxicity evaluation period, up to 3 additional subjects may be accrued at the current dose. These additional subjects will not count towards the formal plan of stopping at two or more toxicity occurrences, but will contribute to the judgment as to the MTD.

We will also conduct some descriptive analyses that will help in the design of a possible phase-II trial. Among patients at the MTD in each arm, we will estimate the proportion with complete or partial response, as well as the median survival (through the Kaplan-Meier method). We will also compute associated 95% confidence intervals, although we realize that they will be very wide (given that we only anticipate 6-8 patients to be treated at the MTD in each arm). The estimates themselves, however, will help in the sample size calculations of possible future phase-II trials.

Progression free survival and overall survival will be measured from the date of starting study treatment (first day of radiation treatment). Progression free survival will be assessed by the treating physician based on the brain MRI.

7.3 Subject Population(s) for Analysis

All subjects who received the radiation treatment per the protocol and concurrent Alisertib will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses.

8.0 SAFETY AND ADVERSE EVENTS

8.1 Definitions

Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in

severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious.

A **serious adverse** event is any AE that is:

- fatal
- life-threatening
- requires or prolongs a hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last day of treatment (radiation treatment and/or Alisertib).

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings or abnormalities that meet the definition of an adverse event must also be recorded and documented as adverse events.

Post-study Adverse Event
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedure results should be grouped under one diagnosis and recorded in the source document.

All adverse events occurring during the study period must be recorded (see Appendix III).

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Unblinding Procedures
This study is not blinded.

8.4 Stopping Rules
Enrollment will stop if there are two or more DLTs in any one dose cohort and the MTD will be defined as the next lowest dose.

8.5 Data and Safety Monitoring Plan
It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the compliance and implementation of the KCC data and safety-monitoring plan (DSMP). Medical monitoring will include a regular assessment of the number and type of serious adverse events by both the assigned Medical Monitor and the KCC DSMC.

8.5.1 Medical Monitoring and AE/SAE Reporting
A Medical Monitor is assigned to this study at the Thomas Jefferson University. This is a physician or pharmacist who is not directly involved in the trial, and is not currently collaborating with the sponsor/investigator on any other trial. The role of the Medical Monitor is to review all reportable AEs and SAEs (in real-time) including grading, toxicity assignments, non-reportable AEs (quarterly), protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial occurring at Thomas Jefferson University. The Medical Monitor may recommend reporting of adverse events and relevant safety data, and may also recommend suspension or termination of the study to the DSMC and TJU IRB.

Every KCC investigator initiated protocol includes requirements for reporting of adverse events based on CTC 4.0. All events are reported to the IRB and Medical Monitor using a password protected web-site. In addition all unexpected and serious adverse events (SAEs) are reported to the TJU IRB and to the Food and Drug Administration (FDA) if applicable. The investigator is required to submit all unexpected and serious adverse events to the TJU IRB and the Medical Monitor within the timeframes outlined in the below table. All AE/SAEs will be reported to the DSMC at the quarterly DSMC review meetings; however, if the Medical Monitor determines corrective action is necessary, an "ad hoc" DSMC meeting will be called. **Fatal adverse events related to treatment which are unexpected must be reported within 24 hours to the TJU IRB and the DSMC. Fatalities not related to the study drug/device must be reported within 5 days.** A summary of the reporting requirements for KCC investigator initiated Phase I and

Phase II studies are presented below.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 and 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 - 48 Hours (Death: 24 Hours) Phase 2 - 5 Working Days
Possible Probable Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 working days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase 1 - 48 Hours Phase 2 - 5 Working Days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase 1 and Phase 2 - 48 Hours (Death: 24 Hours)

**NOTE: This table is based on the NCI AE/SAE reporting Guidelines and the TJU IRB Policy and Procedures. Please follow the individual protocol AE/SAE reporting guidelines if more stringent reporting procedures are specified.

In accordance with 21 CFR 212.32, sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of Alisertib. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Such reports are to be telephoned or faxed to the FDA within 7 calendar days and Millennium within 24 hours of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of Alisertib. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Millennium, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports:

1 (800) FDA - 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

Millennium Pharmacovigilance
SAE and Pregnancy Reporting Contact Information:
North America
PPD, Inc.
Safety and Medical Management, US
Fax: +1 888-488-9697
Hotline number (available 24/7): 1-800-201-8725

AND

Thomas Jefferson University IRB

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 must permanently discontinue study drug(s). All pregnancies and suspected pregnancies must be reported to Millennium Pharmacovigilance (or designee) immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to Millennium Pharmacovigilance (or designee) immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

IND Annual Reports
In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the

Sponsor-Investigator should be copied to Millennium. Copies of such reports should be mailed to:

Millennium Pharmacovigilance

8.5.2 Data and Safety Monitoring Committee

Data and Safety Monitoring Committee (DSMC) is the Data and Safety Monitoring Board (DSMB) for the KCC. The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials at the Thomas Jefferson University KCC. The committee meets quarterly to review the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

- The DSMC meets quarterly. Additional DSMC meetings are scheduled based on the nature and number of trials being monitored over a specified time period. The DSMC meets (by conference call) within 24 hours following the notification of an unexpected adverse event felt to be related to the study drug.
- Prior to each DSMC meeting, each board member, is provided a printout of all reported AEs and SAEs occurring during the reporting period for this clinical trial. The principal investigator provides a detailed and comprehensive narrative assessment of current adverse events to date, indicating their possible significance and whether these toxicities have affected the conduct of the trial. DSMC members are provided with the principal investigator's assessment, a written report summarizing adverse events, safety data, and activity data observed during the specified time period described in each protocol, as well as recommendations from the Medical Monitor. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study.
- A summary of the board's action is sent to each investigator, the CCRRC and TJU IRBs. The DSMC actions may include recommendations and/or requirements that will lead to improved patient safety and/or efficacy, significant benefits or risks that have developed, or other changes determined to be necessary. The DSMC may also take note of slow accrual or lack of scientific progress, and refer such issues to the CCRRC. The DSMC provides the investigator with the rationale for any decision made.

8.6 Product Compliance

A product complaint is a verbal, written, or electronic expression that 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 below) 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.

For Product Complaints,
call MedComm Solutions at
877-674-3784 (877 MPI DRUG)
(US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to PPD (refer to Section 8.2).

9.0 DATA HANDLING AND RECOND KEEPING

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Please see Appendix VI for CRF.

9.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after

the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

10.0 STUDY MONITORING, AUDITING AND INSPECTING

10.1 Study Monitoring Plan

The investigator will allocate adequate time for monitoring activities. The Investigator will also ensure that the medical monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

KCC Investigator Initiated Phase I Studies

Phase I studies require continuous monitoring by the PI of the study with quarterly safety and monitoring reports submitted to the CRMO and the DSMC. Each protocol is assigned to a medical monitor (a member of the Jefferson DSMC who is not directly involved in this trial, and who is a full voting member of the Jefferson DSMC). The medical monitor reviews all adverse events (in addition to unexpected adverse events), safety data and activity data observed in the ongoing clinical trial at each new dose level, prior to dose escalation.

The PI provides a report to the DSMC of all AE/SAEs, safety and toxicity data, and any corrective action that occurred on a quarterly basis. The medical monitor also provides a summary of their review. The summary of all discussions of adverse events are submitted to the DSMC, and these reports are reviewed during the DSMC meetings that take place quarterly. Patients are only identified by initials, and no other personal health information (PHI) is included in the reports.

The medical monitor may recommend reporting adverse events and relevant safety data not previously reported, and may recommend suspension or termination of the trial based on their review of AE/SAE data observed throughout the life of a clinical trial. In such circumstances, and "ad hoc" DSMC meeting will be called to discuss corrective action with the PI. If for any reason the PI of the trial disagrees with the conclusions of the Medical Monitor or DSMC, the issue will be referred to the Associate Director of Clinical Investigations, who will be responsible for dispute resolution.

The summary of all discussions of adverse events are included in the KCC investigator's reports to the TJU IRBs as part of its annual progress report. The DSMC and the TJU IRBs may, based on the monitor's recommendation, suspend or terminate the trial. The quarterly safety and monitoring reports include a statement as to whether this data has invoked any stopping criteria in the clinical protocol.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data

etc.) by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

10.2.1 Independent External and Internal Audits

In addition to review by the DSMC, all studies initiated by KCC investigators are audited by an independent auditor once they have achieved 10% of target accrual. However, a study can be audited at any time based on recommendations by the IRB, DSMC, CCRRC and/or the Director of Clinical Investigations, KCC. Studies are re-audited once they have achieved 50% of target accrual. Special audits may be recommended by the IRB, DSMC or CCRRC based on prior findings, allegations of scientific misconduct and where significant irregularities are found through quality control procedures. Any irregularities identified as part of this process would result in a full audit of that study.

In addition to the audits at 10% and 50%, the CRMO randomly audits at least 10 percent of all patients entered into therapeutic KCC trials and other trials as necessary, on at least a bi-annual basis, to verify that there is a signed and dated patient consent form, the patient has met the eligibility criteria, and that SAEs are documented and reported to the TJU IRB.

All audit reports are submitted to the DSMC for review and action (when appropriate). A copy of this report and recommended DSMC action is sent to the CCRRC and TJU IRB. The committee regards the scientific review process as dynamic and constructive rather than punitive. The review process is designed to assist Principal Investigators in ensuring the safety of study subjects and the adequacy and accuracy of any data generated. The TJU IRB may, based on the DSMC and auditor's recommendation, suspend or terminate the trial.

11.0 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator before commencement of this study.

All subjects for this study will be provided a consent form that is compliant with local and federal regulations, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure.

This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

12.0 STUDY FINANCES

12.1 Funding Source

This study is funded by Millennium.

12.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

12.3 Subject stipends or Payments

There are no subject stipends or payments.

13.0 Publication Plan

Any formal presentation or publication of data from this trial may be published after review and comment by Millennium and prior to any outside submission. Millennium must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Millennium' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Millennium and, in accord with the trial contract and shall not permit disclosure of Millennium confidential or proprietary information.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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15.0 Appendices

Appendix I ECOG Performance status scale

Appendix II Visit Schedule

Appendix III SAE form

Appendix IV MMSE

Appendix V QoL forms

Appendix VI Case Report Forms

Appendix I: ECOG Performance Status

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self- care. Totally confined to bed or chair.
5	Dead

Appendix II: Visit Schedule

	Prior to Registration	Pre-treatment	Concurrent phase		Observation phase	Maintenance phase	Recommended Follow up
Time (day)	-14 to -1	-30 to -1	1-7	8-14	Day 13-42	From Day 43 to 1 year	Year 2 and onwards
Informed consent	X						
Demographics	X						
Medical history	X	X					
H & P	X	X	X[7]	X[7]	X[5]	Q 2 months	X[6]
Neuro exam	X	X	X[8]	X[7]	X[5]	Q 2 months	X[6]
MMSE		X			X[5]	Q 2 months	X[6]
QoL		X			X[5]	Q 2 months	X[6]
Vitals		X	X[7]	X[7]	X[5]	Q 2 months	X[6]
Weight		X	X[7]	X[7]	X[5]	Q 2 months	X[6]
KP/ECOG	X	X	X	X[7]	X[5]	Q 2 months	X[6]
CBC w diff	X	X	X[7]	X[7]	X[5]	Weekly[8]	X[6]
CMP, Mg +	X	X	X[8]	X[7]	X[5]	Q 2 months	X[6]
PT/PTT/INR		X					
Lipid Panel			X[7]	X[7]	X[5]	Q 2 months	
EKG		X					
b-HCG	X[9]						
MRI Brain		X			X[1]	Q 2 months	X[6]
Treatment:							
RT			X[2]	X[2]			
MLN8237			X[3]	X[3]		X[4]	

Q = every
H & P = History & Physical

NOTE:
1. Brain MRI should be done between days 35-42, then every 2 months for 1st year.
2. RT: daily on weekdays for a total of 10 treatments.
3. Alisertib: BID on days of RT only.
4. Alisertib: 50 mg BID on days 1-7 every 21 days, for up to 18 cycles or until progression.
5. Between day 39 to day 45 (at the end of 30 day observation period), then every 2 months
6. Every 3 months from year 1 to year 2, then every 4-6 months afterwards.
7. All items only need to be done at least once during week 1 and at least once during week 2.
8. Until discontinuation of Alisertib.
9. Pregnancy test should be done within 7 days prior to registration, if applicable

Appendix III: SAE FORM

Serious Adverse Event Form

Protocol # ______________________________	Subject ID: ___________________________________
Site # ________________________________	Subject Initials: _______________________________

Investigator Information		Patient Information	
Date of report: _____/_____/_____ (dd mmm yyyy)	Report type: ❑ Initial ❑ Follow-up	Date of birth _____/_____/_____ (dd mmm yyyy)	Race: ❑White ❑Black ❑Hispanic ❑American Indian or Alaskan Native ❑Asian or Pacific Islander ❑Other_________
Principal Investigator's Name:	Tel. # (____)______________	Gender: ❑ Male ❑ Female	
Principal Investigator's Address:	Fax # (____)______________	Height: _____ cm /**or** _____ in	
	Email: ___________________	Weight: _____ kg /**or** _____ lb	

Study Drug Information				
Indication for use:		Indication diagnosis date: _____/_____/_____ (dd mmm yyyy)		
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:
Study drug name:	Regimen:	Dose and unit:	Date of first dose:	Date of last dose prior to event:

Medical history and laboratory/diagnostic tests

Please provide or attach *anonymized* relevant data regarding:

- Past medical and allergy history
- History of past therapy for indication for use
- Concomitant medication
- Relevant laboratory and diagnostic tests

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If more than one serious adverse event, please copy this page and complete all fields on page individually for each SAE

Serious Adverse Event: _____

SAE onset date: _____/_____/_____ (dd / mmm / yyyy)

Did SAE(s) abate after stopping study drug? ❑ Yes ❑ No ❑ NA

Did SAE(s) reappear after reintroducing study drug? ❑ Yes ❑ No ❑ NA

Serious Criteria (check all that apply):

- ❑ Death
- ❑ Life threatening
- ❑ Hospitalization / prolonged hospitalization
- ❑ Persistent or significant disability / incapacity
- ❑ Congenital anomaly / birth defect
- ❑ Important medical event

Maximum Intensity:

- ❑ Grade 1 / Mild
- ❑ Grade 2 / Moderate
- ❑ Grade 3 / Severe
- ❑ Grade 4
- ❑ Grade 5

Action taken with study drug (check all that apply):

Drug(s)

_____ ❑ Dose continued unchanged

_____ ❑ Dose reduced. Date decreased: _____/_____/_____ (dd / mmm / yyyy)

_____ ❑ Dose increased. Date increased: _____/_____/_____ (dd / mmm / yyyy)

_____ ❑ Dose delayed. Date held: _____/_____/_____ (dd / mmm / yyyy)

_____ ❑ Discontinued permanently due to this SAE. _____/_____/_____ (dd / mmm / yyyy)

_____ ❑ Not applicable, patient no longer receiving study drug.

Status of SAE at time of this report:

- ❑ Fatal
- ❑ Completely resolved ____/____/____ (dd / mmm / yyyy)
- ❑ Resolved with sequelae ____/____/____ (dd / mmm / yyyy)
- ❑ Not completely resolved
  - ❍ ongoing and unchanged
  - ❍ ongoing with increased intensity
  - ❍ ongoing with decreased intensity

Study Drug	Is there a reasonable possibility that the event is associated with this study medication?	
1. _____	❑ Yes	❑ No
2. _____	❑ Yes	❑ No
3. _____	❑ Yes	❑ No
4. _____	❑ Yes	❑ No
5. _____	❑ Yes	❑ No
6. _____	❑ Yes	❑ No
7. _____	❑ Yes	❑ No
8. _____	❑ Yes	❑ No
9. _____	❑ Yes	❑ No

Is there a reasonable possibility that the event is associated with:

- ❑ Non-study drug, procedure, or therapy *Specify:* _____
- ❑ Another alternative etiology (e.g. indication for use, intercurrent illness) *Specify:* _____
- ❑ Protocol design or procedures (alone or in addition to study drug) *Specify:* _____

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Description of Serious Adverse Event(s)

Please provide a brief narrative description of the SAE (presenting symptoms, clinical course, treatment, etc.). or attach extra pages, if available.

Death Information

Date of death: _____/_____/_____
dd mmm yyyy

Autopsy performed? ❑ Yes ❑ No

If yes, autopsy report attached? ❑ Yes ❑ No

Cause(s) of death (list primary cause of death first):

_____

_____

_____

Was the patient's death related to:

Study drug(s)? ❑ Yes ❑ No If yes, please specify all that apply _____

_____

Protocol design or procedures (alone or in addition to study drug)? ❑ Yes ❑ No If yes, please specify _____

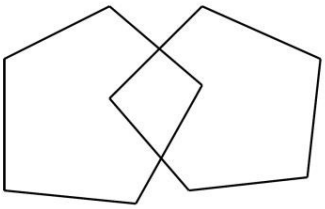
_____

Study contact completing form printed name	Study contact completing form signature	Date (dd/mmm/yyyy)
Principal investigator printed name	Principal investigator signature	Date (dd/mmm/yyyy)

SAEF (Version 13Feb2008 IIS)

Appendix IV: MMSE

Mini-Mental State Examination

ITEM	Maximum Score	Actual Score
ORIENTATION		
What is the (year) (season) (date) (day) (month)?	5	( )
Where are we: (state) (city) (hospital)?	5	( )
What (street) do you live on? What (county)?		
REGISTRATION		
Name 3 objects (apple, penny, table): 1 second to say each. then ask patient all three after you have said them. Give 1 point for each correct answer. Then repeat them until all three are learned (for later checking).	3	( )
ATTENTION AND CALCULATION		
Serial 7s. Give 1 point for each correct answer. Stop after 5 answers. Spell "WORLD" backwards: "DLROW". Score whichever is highest.	5	( )
RECALL		
Ask for the three objects repeated above. Give 1 point for each correct.	3	( )
LANGUAGE		
Show 2 objects (pencil and watch); ask for their names.	2	( )
Repeat the following: **"No ifs, ands, or buts."**	1	( )
Follow a 3-stage command: "Take a paper in your right hand, fold it in half, and put it on the floor."	3	( )
Have the patient read and obey the following:		
"CLOSE YOUR EYES"	1	( )
Have the patient write a sentence of his or her own choice.	1	( )
Have the patient copy the following design. 	1	( )
TOTAL SCORE	**30**	( )

Appendix V: QoL forms

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

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

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

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EORTC QLQ - BN20

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

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

Appendix VI: Case Report Form

SCREENING

VISIT DATE : _____

Date Screening Informed Consent Signed: _____ ☐ Not Applicable	Screening Date: _____ ☐ Not Applicable
Is this participant a screen failure? ☐ Yes ☐ No **(If Yes, complete Off Study form)** If yes, specify primary reason for screen failure: ☐ Investigator decision ☐ Participant decision ☐ Did not meet eligibility criteria ☐ Other, specify: Comments:	
Who referred participant?	☐ Physician ☐ Health Care Provider ☐ Family/friend ☐ Self ☐ Other, specify:
How did participant find out about the study?	☐ Physician Nurse ☐ Family/friend ☐ NCI web site ☐ Written material ☐ Unknown ☐ Other, specify: ☐

INCLUSION CRITERIA

	Criteria	Yes	No	N/A
1	Patients must have a previously histologically or cytologically confirmed high grade glioma (astrocytic or oligodendroglial supratentorial tumors grade 3 or 4) that has been previously treated with fractionated radiation therapy and now shows evidence of recurrence.			
2	Patients must have recovered from the toxic effects of prior therapy.			
3	Patients must have recovered from the effects of surgery. There must be a minimum of 21 days from the day of surgery to the day of protocol treatment. For core or needle biopsy, a minimum of 7 days must have elapsed prior to the day of protocol treatment.			
4	Prior treatment with cytotoxic and biological agents is permissible. There should be at least a 2 week break between prior treatment and the protocol treatment.			
5	Prior treatment with fractionated radiation therapy (up to 60Gy) is an eligibility criterion, however there should not have been a second course of fractionated radiotherapy to the supratentorial area.			
6	One prior single fraction radiosurgical procedure within the treatment field is acceptable if V12<5 cc (V12 is the volume of normal brain (outside GTV) receiving 12 or more Gy). Additional radiosurgical procedures outside of the treatment area are acceptable.			
7	Subject must be able to take oral medication and to maintain a fast is required for 2 hours before and 1 hour after MLN8237 administration.			
8	ANC > 1500/mm³, platelets > 100,000/mm³, Hgb > 9 g/dL. Values must be obtained without need for myeloid growth factor or platelet transfusion support within 14 days of registration, however, erythrocyte growth factor is allowed as per published ASCO guidelines.			
9	Total bilirubin ≤ ULN, SGOT (AST) and SGPT (ALT)< 1.5 x ULN, within 14 days of registration.			
10	Adequate renal mL/minute (Cockcroft-Gault), within 14 days of registration.			
11	Age >18 years.			
12	ECOG performance status <2 (see Appendix I).			
13	Life expectancy of greater than 2 months.			
14	Women of childbearing potential must have a negative β-HCG pregnancy test documented within 7 days prior to registration.			
15	Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.			
16	Ability to understand and the willingness to sign a written informed consent document.			

EXCLUSION CRITERIA

	Criteria	Yes	No	N/A
2	Known history of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease; requirement for supplemental oxygen.			
3	Systemic infection requiring IV antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.			
4	Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure, 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.			
5	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.			
6	Patient has received other investigational drugs within 14 days before enrollment			
7	Serious medical or psychiatric illness likely to interfere with participation in this clinical study.			
8	Other severe acute or chronic medical or psychiatric condition, including uncontrolled diabetes, malabsorption, resection of the pancreas or upper small bowel, requirement for pancreatic enzymes, any condition that would modify small bowel absorption of oral medications, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for enrollment in this study.			
10	Treatment with clinically significant enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine or phenobarbital, or rifampin, rifabutin, rifapentine or St. John's wort within 14 days prior to the first dose of MLN8237 and during the study.			
11	Known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C. Testing is not required in the absence of clinical findings or suspicion.			
12	Patients have a history of any other malignancy from which the patient has been disease-free for less than 2 years, with the exception of adequately treated basal or squamous cell carcinoma of skin, superficial bladder cancer or carcinoma in situ of cervix, AJCC (version 7.0) stage 0 or I breast cancer, AJCC (version 7.0) stage I, or II prostate cancer.			
13	Radiation therapy to more than 25% of the bone marrow. Whole pelvic radiation is considered to be over 25%.			

REGISTRATION

Gender: ☐Male ☐Female ☐Unknown ☐ Unspecified	Date of Birth: _____
Race: ☐White *(Check all that apply)* ☐Black or African American ☐Native Hawaiian or Other Pacific Islander ☐Asian ☐American Indian or Alaska Native ☐Unknown	Ethnicity: ☐Hispanic or Latino ☐Not Hispanic or Latino ☐Unknown
Date Study Informed Consent Signed: _____	Date of Registration: _____
Does the participant satisfy all of the eligibility criteria? ☐Yes ☐No (If No, complete Off Study form)	

INTERVENTION ADMINISTRATION

Agent #	Agent	Dose	Dose Units	Frequency	I I I	Date Agent Started
1						
2						
3						

BASELINE MEDICAL/SURGICAL HISTORY

Check here if <u>all</u> body systems are normal: ☐

Body System	Normal	Abnormal	Not Assessed	Comments (Required if Abnormal; provide condition/diagnosis)
H/E/E/N/T	☐	☐	☐	
Neck	☐	☐	☐	
Respiratory	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Gastrointestinal	☐	☐	☐	
Musculoskeletal	☐	☐	☐	
Dermatologic	☐	☐	☐	
Hematopoietic/Lymph	☐	☐	☐	
Endocrine/Metabolic	☐	☐	☐	
Genitourinary	☐	☐	☐	
Breasts	☐	☐	☐	
Neurologic	☐	☐	☐	

Does the participant have any allergies? ☐Yes ☐No

If Yes, specify:

_____

BASELINE SYMPTOMS

Check here if none reported (no baseline symptoms):

Symptom Description	Onset Date	Grade*	Comments
*Grade			
1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life Threatening			

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PHYSICAL EXAM

Examination Date *:* _____ ☐Not Done		
Height: _____ ☐cm ☐in ☐Not Obtained	Weight: _____ ☐kg ☐lb ☐Not Obtained	Temperature: _____ ☐°C ☐°F ☐Not Obtained
Pulse Rate: _____ ☐Not Obtained	Respiration Rate: _____ ☐Not Obtained	Blood Pressure: _____ ☐Not Obtained Systolic (mm Hg) Diastolic (mm Hg)
ECOG Performance Status: ☐0 ☐1 ☐2 ☐3 ☐4		

Check here if NO body systems were examined: ☐

Body System/Site	Normal	Abnormal	Not Examined	Comments (Required if Abnormal; provide condition/diagnosis)
Appearance*	☐	☐	☐	
Skin*	☐	☐	☐	
H/E/E/N/T*	☐	☐	☐	
Thyroid	☐	☐	☐	
Chest	☐	☐	☐	
Lungs	☐	☐	☐	
Breasts	☐	☐	☐	
Heart	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal*	☐	☐	☐	
Genitalia	☐	☐	☐	
Pelvis	☐	☐	☐	
Rectal	☐	☐	☐	
Prostate	☐	☐	☐	
Vascular	☐	☐	☐	
Neurological*	☐	☐	☐	
Lymph Nodes	☐	☐	☐	

* Required Assessments

All other Body Systems/Sites are to be done as clinically indicated.

MMSE and QLQ result

*** Attach MMSE and QLQ result here.**

BASELINE IMAGING STUDY PRIOR TO RECEIVING PROTOCOL TREATMENT
(Fill in what is applicable)

*** Please attached MRI, CT, PET/CT report here.**

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CONCOMITANT MEDICATIONS/STEROIDS USE LOG
(medications prescribed during study period)

At end of study only: check this box if participant did not take any concomitant medications

☐ **None**

Date	Medication	Dose	Frequency	Start Date	Stop Date	Continuing
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐
						☐

CLINICAL LABORATORY DATA

* Attached blood test report here.
* Attach EKG report here.

PREGNANCY SPECIMEN DATA

Reason pregnancy data was not collected:

☐ Participant is male

☐ Participant is female and not of childbearing potential

Lab Test	Pregnancy Test Type	Result	Date Specimen Collected
Pregnancy	☐ Urine ☐ Serum	☐ Not Obtained ☐ Positive ☐ Negative	

TREATMENT INTERRUPTION / MODIFICATION FORM

TREATMENT Interruptions:

1		☐ Investigator decision, specify ☐ Participant decision, specify ☐ AE/SAE, specify ☐ Other, specify		☐ Yes ☐ No ☐ N/A	
2		☐ Investigator decision, specify ☐ Participant decision, specify ☐ AE/SAE, specify ☐ Other, specify		☐ Yes ☐ No ☐ N/A	
3		☐ Investigator decision, specify ☐ Participant decision, specify ☐ AE/SAE, specify ☐ Other, specify		☐ Yes ☐ No ☐ N/A	
4		☐ Investigator decision, specify ☐ Participant decision, specify ☐ AE/SAE, specify ☐ Other, specify		☐ Yes ☐ No ☐ N/A	

AE log

Attached AE log form here

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OFF STUDY*

Date On Follow-up: ☐ Not Applicable	Date Off Follow-up: ☐ Not Applicable
Date Off Study:	Date of Last Contact:
Date Last Study Agent Taken: ☐ Not Applicable	

Reason Off Study (Please mark only the primary reason. Reasons **other than Completed Study** require explanation below)

- ☐ Completed study
- ☐ Ineligible
- ☐ AE/SAE **(complete AE CRF & SAE form, if applicable)**
- ☐ Lost to follow-up
- ☐ Non-compliant participant
- ☐ Concomitant medication
- ☐ Medical contraindication
- ☐ Pregnancy
- ☐ Withdraw consent
- ☐ Death **(complete Death Report CRF & SAE form)**
- ☐ Other

Reason Explanation:

_____

*This form must be completed for all participants that have signed an informed consent, including screen failures.

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DEATH REPORT

Date of Death: _____	
Place of Death: ☐ Hospital (Submit discharge summary to NCI, DCP) ☐ Other, specify: _____ ☐ Unknown	Cause of Death: ☐ AE/SAE ☐ Other, specify: _____ ☐ Unknown
Autopsy performed? ☐ Yes (Attached autopsy report here) ☐ No ☐ Unknown	

VERIFICATION

"I have reviewed all the Case Report Forms for the above participant and agree that they are accurate and complete."

_____ _____

Investigator's Signature Date

_____

Investigator Name (PLEASE PRINT)