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Title: Phase II Clinical Trial of Marizomib for Recurrent Low-Grade and Anaplastic Supratentorial, Infratentorial and Spinal Cord Ependymoma

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Drug Name:	Marizomib
IND Number:	139633
Sponsor:	CCR, NCI
Manufacturer:	Celgene/Triphase

Commercial Agents: None

PRÉCIS

Background:

- Ependymomas are rare primary brain tumors arising from radial glial stem cells. They comprise 5.2% of all pediatric primary brain tumors and 1.9% of all adult primary brain tumors.
- The standard therapy for newly diagnosed ependymoma is gross total resection followed by radiation therapy. For anaplastic ependymoma, recurrence rate is high with a median progression free survival (PFS) of 2.3 years.
- There are limited chemotherapy options for recurrent ependymomas, which have already been irradiated. Therefore, there is an unmet need to target novel pathways for treatment of ependymomas.
- About 70% of supratentorial ependymomas have a characteristic signature *C11orf95-RELA* fusion which drives tumorigenesis in ependymomas by activating the NF-KB transcription pathway.
- Marizomib is a second-generation irreversible proteasome inhibitor which penetrates across the blood-brain-barrier (BBB). It inhibits the activity of 20S proteasome in glioma cells, activates caspases, builds up reactive oxygen species and thus induces apoptosis. Marizomib blocks the NF-pathway by proteasome inhibition. Thus, it may have an additional targeted therapeutic effect in the *RELA*-fusion molecular subgroup of ependymomas.

Objective:

- To evaluate the efficacy of treatment with marizomib in *RELA*-fusion recurrent ependymoma and non *RELA*-fusion recurrent ependymoma as measured by progression-free survival at 6 months (PFS6).

Eligibility:

- Histologically proven intra-cranial or spinal ependymoma.
- Radiographic evidence of tumor progression
- Patients must be ≥ 18 years old.
- Patients must have had prior radiotherapy.

Design:

- This is a phase II study to determine the efficacy of marizomib in recurrent ependymoma.
- A novel 2-stage sequential design will be employed to conduct the trial for recurrent ependymoma.
- In the first stage, we will enroll 18 patients with *RELA*-fusion ependymoma and if 4 or more patients in Cohort 1 are progression free at 6 months, we will proceed to stage 2; otherwise we will terminate the trial and conclude that marizomib is not effective.
- In the second stage, we will enroll 32 patients with non *RELA*-fusion ependymoma.
- Patients will be treated with marizomib in cycles consistent of 28 days until disease progression or a maximum of 24 cycles.

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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To evaluate the efficacy of treatment with marizomib in *RELA*-fusion recurrent ependymoma and non *RELA*-fusion recurrent ependymoma as measured by progression-free survival at 6 months (PFS6).

1.1.2 Secondary Objective(s)

- To estimate the 12-month progression-free survival (PFS12), median progression-free survival (PFS) and overall survival (OS) of *RELA*-fusion and non *RELA*-fusion recurrent ependymoma patients treated with marizomib.
- To estimate the efficacy of marizomib in recurrent ependymoma patients (*RELA*-fusion Cohort 2 and non *RELA*-fusion Cohort 4) with more than 2 prior chemotherapies as measured by PFS6, PFS12, median PFS and OS.
- To estimate the efficacy of marizomib in recurrent ependymoma patients (*RELA*-fusion Cohort 2 and non *RELA*-fusion Cohort 4) with more than 2 prior chemotherapies as measured by objective response.
- To determine the safety of marizomib in recurrent ependymoma patients and in a subset of patients with more than 2 prior chemotherapies (RELA-fusion Cohort 2 and non-RELA-fusion Cohort 4).
- To longitudinally evaluate patient reported outcome measures using self-reported symptom severity and interference with daily activities using the MDASI-BT and/or MDASI-SP instrument.

1.1.3 Exploratory Objective(s)

- To determine if there is a correlation with response rate to presence of the RELA gene fusion in pathology from surgical CNS tissue specimen.
- To assess tumor tissue for biomarkers (gene mutations, copy number alterations and fusions) using the neuro-oncology brain primary CNS panel.
- To assess expression of NF-κB pathway using RNA sequencing on tumor tissue.
- To assess single nucleotide polymorphisms from germline DNA to establish a genetic association with CNS adverse events.

1.2 BACKGROUND AND RATIONALE

1.2.1 Background on Ependymomas

Ependymomas are rare glial tumors which can arise in the brain or the spinal cord. While historically they were thought to originate from the wall of the ventricles or the spinal cord, recent studies have shown that they originate from the radial glial stem cells [1]. Microscopically, they are composed of uniform small cells with round nuclei in a fibrillary matrix and are characterized by the presence of perivascular anucleate zones called perivascular pseudo rosettes [2]. Less frequently true ependymal rosettes consisting of ependymal cells arranged around a central lumen may be present. Ependymomas account for 2-9% of all neuroepithelial tumors [3]. While they can occur in all age groups, they are more common in children than adults. They comprise 5.2% of all pediatric primary brain tumors and 1.9% of all adult

primary brain tumors [2]. In children less than 3 years, ependymomas make up to 30% of all intracranial tumors and are the second most common intracranial malignancy [3, 4]. In adults, ependymomas are the commonest spinal cord neuroepithelial tumors, comprising 50 to 60% of all spinal gliomas [5]. Ependymomas are more prevalent in males as compared to female patients and in whites as compared to African Americans [4].

The previous WHO classifications, traditionally divided ependymomas into grade I, grade II or grade III based on histopathology. Grade I ependymomas comprise sub ependymomas and myxopapillary ependymomas, which are slow growing and often considered benign, although once disseminated, myxopapillary ependymomas are incurable. Grade II ependymomas are simply called ependymomas. Grade III ependymomas are also called anaplastic ependymomas. The 2016 WHO classification of brain and central nervous system tumors, recognizes the molecular basis of tumorigenesis and incorporates these molecular findings along with histopathologic findings to establish an integrated diagnosis of ependymomas. Now ependymomas are divided into 9 molecular groups based on histology and location. In contrast to the inconsistent relationship observed between pathological values and outcomes, the current integrated classification refines the prognosis of ependymomas based on age, location and molecular features.

Based on anatomical location, ependymomas can be classified into supratentorial, posterior fossa or spinal cord ependymomas. A distinct pathological entity recognized in the WHO 2016 classification of CNS tumors is the *RELA*-fusion ependymoma. *RELA*-fusion ependymomas occur supratentorially. About 70% of *RELA*-fusion ependymomas are found in children and a lower proportion are present in adults [6]. Whole genome sequencing of these tumors revealed the occurrence of chromothripsis within chromosome 11q12.1-q13.3 [6]. Chromothripsis a genetic phenomenon which causes shattering and clustered rearrangements of genes leading to oncogenic fusion products. The reordered chromosomal products in this region form a poorly characterized gene, *C11orf95* to *RELA* [6]. The fusion transcript of this gene codes a transcription factor p65, also known as RelA which is a key effector in the NF-κB pathway [2, 7]. Thus, patients with RELA fusion ependymomas have a constitutive activation of the NF-κB pathway.

1.2.1.1 The NF-κB pathway

NF-κB is an inducible transcription factor which was discovered as a regulator of expression of the κ light chain gene in B cells [8]. NF-κB plays an important role in regulating immune response and influences gene expression related to cell survival, differentiation and proliferation. The NF-κB family members consist of RelA/p65, RelB, c-Rel, p50 [NF-κB1] and p52 [NF-κB2]. The core elements of NF-κB pathway are the NF-κB transcription factor, the inhibitory IκB protein and the IκB (IKK) kinase complex. In the resting state, the NF-κB dimers are held dormant in cytoplasm through a non-covalent association with IκB proteins. This association prevents the NF-κB nuclear translocation and DNA-binding activity. When the cell is stimulated with external stimuli such as pro-inflammatory cytokines, e.g. tumor necrosis factor receptor and interleukin-1 receptor or any other stressors, the IKK complex is activated. The activated IKK complex leads to the phosphorylation, ubiquitination and deactivation of IκB. This releases the NF-κB dimers to translocate to the nucleus and promote transcription of the pro-survival genes [8, 9].

1.2.1.2 The Ubiquitin-Proteasome System

The ubiquitin-proteasome system (UPS) is a highly conserved key pathway which causes the intracellular degradation of proteins. Through this role, UPS regulates cell-cycle control, transcription and other cellular events and thus maintains normal cell functioning [10]. The mammalian 26S proteasome consists

of a 20S proteolytic core flanked by two 19S regulatory caps. The process of cellular protein degradation occurs in a two-step process. First, ubiquitin is linked to the lysine residues in proteins via a cascade of enzymatic reactions to form poly-ubiquitinated chains. In the second step, proteins tagged with this ubiquitin conjugates are marked for degradation through the 26S proteasome [11]. The 19S regulatory particles, bind to the poly-ubiquitinated proteins and send them to the 20S proteasome core. Inside the 20S core, the protein is degraded into small peptides using 3 catalytic enzymes: chymotrypsin-like (CT-L), trypsin-like (T-L) and caspase-like (C-L) and the ubiquitin is released for recycling [12]. While previously the function of the ubiquitin-proteasome system was thought to be confined to the role of degradation of damaged intracellular proteins, it is now understood that this system plays an integral role in the turn-over of short-lived regulatory proteins which control cell division, growth, transcription and signaling. Defects in this intricate pathway are associated with many diseases and cancer. Studies have shown that cancer cells evade apoptosis by altering the normal proteasome pathway [11] and are more vulnerable to proteasome inhibition [12]. The interest in proteasome inhibitors as a potential cancer therapeutic agent was generated when it was found that proteasome inhibitors induced apoptosis in leukemic cell lines [13, 14] and an *in vitro* model of Burkitt's lymphoma [15]. Evidence of anti-neoplastic activity of proteasome inhibitors has been found in solid tumors including gliomas and prostate cancer [16, 17]. A major mechanism of action of proteasome inhibitors is the inhibition of NF-κB transcription factor, through the stabilization of its inhibitor IκB protein.

1.2.2 Rationale for Marizomib

Even though in vitro studies have established the potential of proteasome inhibitors as anti-neoplastic drugs, the translation of these agents into clinical practice has been challenging due to a relative lack of potency, selectivity or stability [12]. In brain tumor patients, the primary challenge is getting the drug through the Blood Brain Barrier (BBB). Early proteasome inhibitors like bortezomib and carfilzomib have peptide-based structures and cannot cross the BBB which limits their application for central nervous system tumors. Marizomib, also known as salinosporamide A or NPI-0052, is a second-generation proteasome inhibitor with penetration across the BBB [16]. Marizomib is a potent irreversible inhibitor of the 20S and has all 3 enzyme activities of the 20S proteasome – CT-L, T-L and C-L as compared to bortezomib which has reversible activity predominantly against the CT-L subunit [16]. It leads to the inhibition of both inducible and constitutive activation of NF-κB in cancer cells [18]. Marizomib also induces cell apoptosis through several additional mechanisms: 1) activation of caspase-3, caspase-8, caspase-9 and poly (ADP-ribose) polymerase (PARP) cleavage, 2) potentiation of apoptosis induced by tumor necrosis factor (TNF) and suppression of TNF-induced cell invasion, 3) generation of reactive oxygen species (ROS) via an increase of superoxide production 4) reduction of the potential of mitochondrial membrane 5) release of apoptogenic protein cytochrome-c (cyto-c) and second mitochondrial activation of caspases (Smac) from mitochondria to cytosol, 6) up-regulation of endoplasmic reticulum stress related proteins [16, 18].

1.2.3 Pre-Clinical data

A recent preclinical study tested the in-vitro activity of marizomib in malignant glioma cell lines U-251 and D-54 [16]. It was found that marizomib profoundly inhibited the CT-L activity of the 20S proteasome in both cell lines. The half maximal inhibitory concentration (IC50) was measured as 52nM for U-251 and 20nM for D-54 [16]. It was also observed that in-vitro, marizomib induced apoptosis and increased ROS generation in glioma cells. In a murine model, it was seen after an injection of ^{3}H labelled marizomib, the CNS distribution of radioactivity was ~30% of that for steady-state blood level, thus confirming the penetration of marizomib across the BBB [16].

Although the rationale for testing marizomib for ependymomas harboring the RELA fusion is very strong, as described above, there are additional preclinical data that suggests that proteasome inhibition may be an effective treatment of other ependymomas. A preclinical model was developed by the Gilbertson lab by amplifying Ephb2 in radial glial stems, the precursor cells of ependymoma. These cells were then subject to high throughput screen using the FDA approved drug library [19]. Proteosome inhibitors were among the most active in this model system, including xenograft intracranial models. However, this class of drug was not recommended for further investigation in ependymoma because the existing agents at the time (ie bortezomab) were designed NOT to cross the blood-brain barrier. Marizomib effectively crosses the BBB, thereby making it a logical treatment option with this robust preclinical data.

Recently, a genetically engineered mouse model (GEMM) was created by Dr. Eric Holland (personal communication). Using the RCAS/tva system, he was able to reproduce the RELA-C11orf95 fusion that drives the development of this subtype of ependymoma. As illustrated below in Figure 1, there is prominent development of an intracranial tumor in this mouse model system. Furthermore, as shown in Figure 2, treatment of mice with established intracranial RELA-fusion tumors with marizomib resulted in tumor response, which can be dramatic. These results further support testing marizomib in patients with ependymoma.

Figure 1

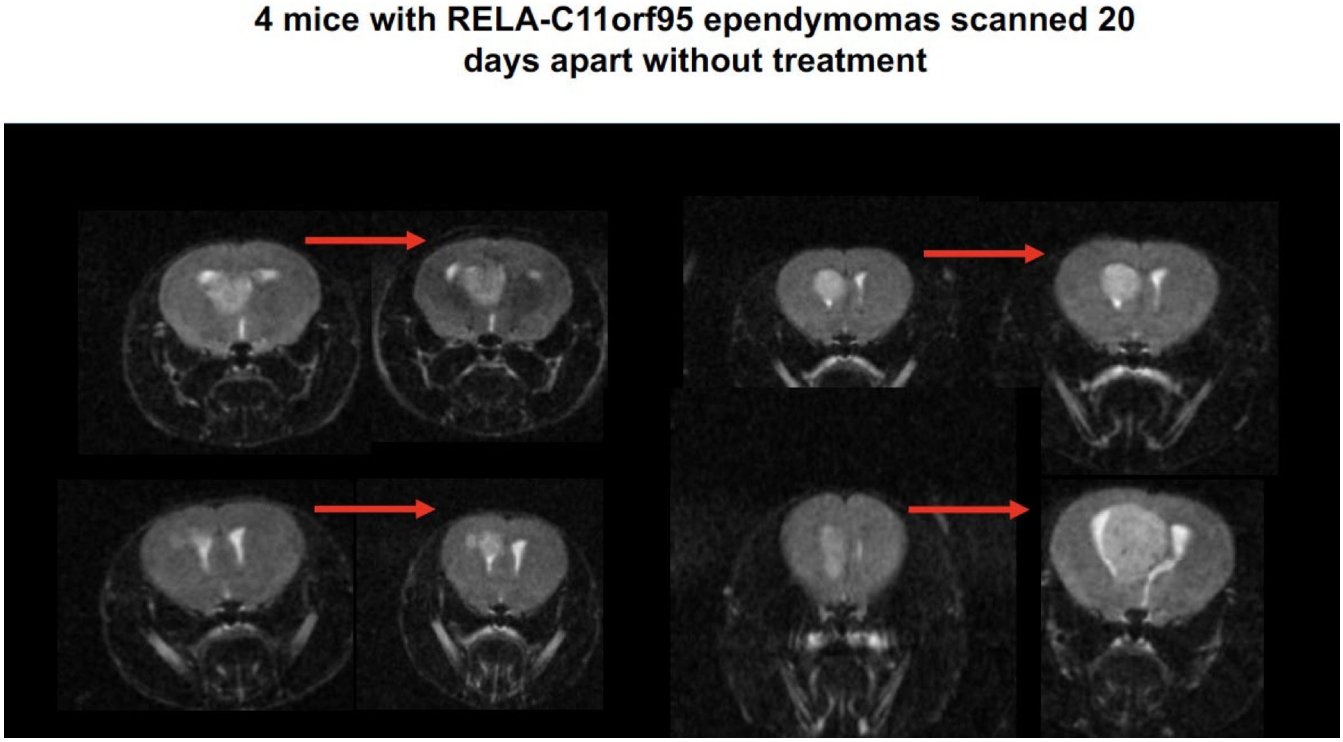
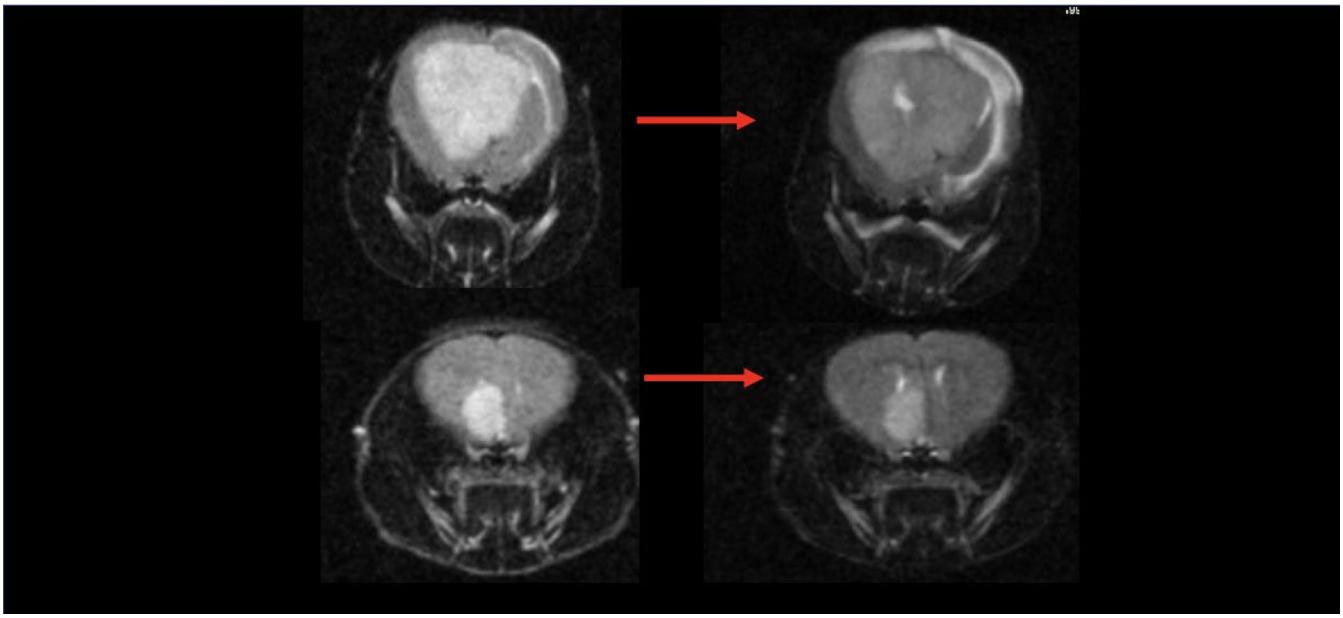


Figure 2

2 mice with RELA-C11orf95 ependymomas scanned 20 days apart on treatment with Marizomib



1.2.4 Clinical data

A phase I clinical study in eighty-six patients with advanced malignancies including multiple myeloma used marizomib in 4-week cycles testing doses between 0.1 – 0.9 mg/m^2 over 1 to 10 minutes administered on day 1,8, 15 and another schedule which tested doses 0.075 – 0.6 mg/m^2 over 1 to 120 minutes, given on day 1,4, 8, 11 in 3-week cycles [20]. The most common related adverse events were nausea, diarrhea, fatigue and infusion site pain. Peripheral neuropathy or hematological toxicity as seen with bortezomib was not observed. There were no grade 4 related-adverse events (AEs). In the first schedule, the recommended phase 2 dose (RP2D) was 0.7 mg/m^2 infused over 10 minutes. In the second schedule, the RP2D was 0.5 mg/m^2 infused over 2 hours in combination with dexamethasone. CNS toxicities were seen with the second schedule when the drug was infused over 10 minutes, likely due to maximal concentration reached towards the end. Dexamethasone was added to the second schedule to prevent toxicity due to immunoglobulin deposition. Hydration was given to all patients before and after the marizomib infusion to prevent acute renal injury. An identical RP2D was established in another phase 1 study [21]. While the regimen of choice for relapsed and refractory multiple myeloma is the second schedule with twice weekly dosing, the once a week dosing every 4-week cycle is being used in NCT02330562 and NCT02903069 which are testing marizomib in patients with glioblastoma. In this proposed study, we will use the RP2D of marizomib 0.8mg/m^2 over 10 minutes IV infusion administered on Days 1,8,15 of each 28-day cycle, which was used in NCT02330562. Dose escalation to 1.0mg/m^2 was not feasible in these adults glioblastoma trials (NCT02330562 and NCT02903069) due to adverse events.

We chose the once a week dosing, on4-week cycles, as it is a more practical dosing schedule in contrast to twice a week dosing on 3-week cycles.

1.2.5 Rationale for this study

Ependymomas are rare tumors, with limited options for treatment once they recur. The standard therapy for newly diagnosed ependymoma is gross total resection followed by radiation therapy. For anaplastic ependymoma, recurrence rate is high with a median progression free survival of 2.3 years [22]. The role of chemotherapy in ependymomas in both upfront or recurrent setting is not well established. There are no prospective clinical trials evaluating the benefit of chemotherapy in adult patients with ependymomas. In children, upfront chemotherapy with alternating courses of procarbazine and carboplatin, etoposide and cisplatin; and vincristine and cyclophosphamide were tried with moderate clinical benefits [23]. While NF-κB mediated tumor proliferation is seen in many cancers, tumorigenesis in *RELA*-fusion ependymoma is driven by NF-κB activation. We postulate that marizomib mediated proteasome inhibition will inhibit the NF-κB pathway and thus lead to tumor cell death. Additionally, given the activity of proteasome inhibitors in glioma cells and other cancers, marizomib may also prove efficacious in non *RELA*-fusion ependymoma.

1.2.5.1 Neurotoxicity's management

Based on findings from preclinical and clinical studies, marizomib, particularly when administered as a 10 minute infusion, crosses the BBB, resulting in multiple CNS AEs ranging in severity from Grade 1 to Grade 4. CNS AEs appear to be dose related as more are observed at the 1.0 mg/m^2 dose and in general, respond to dose reduction. Due to concern for CNS AEs, in this study we will use marizomib at 0.8 mg/m^2 and there will be no dose escalation. CNS AEs are generally treated with dose modifications and appropriate supportive treatments as indicated. If resolution does not occur following these measures, consider underlying disease progression or other causes. The most common CNS AEs include the following:

Hallucinations: Hallucinations are frequently observed in ongoing marizomib studies in glioblastoma ranging in incidence from 19-37%. In general, hallucinations tend to be grade 1 or 2 but one grade 4 event, requiring hospitalization, has been observed. The hallucinations are transient and self-limiting. Visual hallucinations are more common than auditory and there is a trend for increased incidence with age. Hallucinations are frequently more disturbing to the caregiver than to the patient. Hallucinations are usually managed successfully by dose reduction and are an infrequent reason for treatment discontinuation.

Ataxia: Events of gait disturbance, balance disorders/dizziness, and ataxia are frequently observed in the ongoing studies in glioblastoma, MRZ 108 and MRZ 112, with a range of 5-28%. These adverse effects which are cerebellar in nature are suspected to be related to the predominance of proteasomes in the cerebellar region. The events typically occur within the 1st or 2nd cycle, are usually grade 1-2 but events of ataxia have required hospitalization. Patients are treated with dose modifications and steroids as needed without leading to permanent discontinuation of marizomib. As a result of these events, patients are warned not to operate heavy machinery and/or drive if experiencing cerebellar side-effects.

Headache: Headaches have been reported with administration of marizomib across indications and dosages. While headaches are commonly present due to the underlying disease in GBM, in the ongoing studies with marizomib in GBM, incidence of treatment emergent headaches ranges from 25-53%. Dose modifications and treatment with steroids are recommended for management of headaches in glioblastoma.

Confusion: Confusional state has been reported across marizomib studies and dose ranges. In ongoing glioblastoma studies, the incidence of confusional state ranges from 17-28%. Events of confusional state have been reported as SAEs and while most are grade 1-2 in severity, grade 3 events

have been reported. Dose modifications and treatment with steroids are recommended for management of confusion in glioblastoma.

1.2.6 Rationale for patient reported-outcomes

Although rare, ependymal tumors have a recognized impact on the patients' physical and neurologic function [24]. Despite aggressive therapy at diagnosis, many ependymomas recur. Currently, no standard therapy at recurrence has been established, and the impact of chemotherapy at recurrence has been limited [2, 24].

This study seeks to establish effective therapies at recurrence and improve on current clinical results. We hypothesize that treatment with marizomib will result in improved survival. However, given the intensive nature of this regimen, it will be important to determine whether any determined survival benefit is associated with improvements in symptoms or does a worsening of these parameters offset the increase in survival.

Precedence for measuring "non-therapeutic" endpoints exists in oncology research. For example, Gemcitabine was approved by the FDA partially as a consequence of the decrease in pain reported in pancreatic patients who were treated, not on the basis of survival improvement which was modest, at best. There have been efforts in neuro-oncology to evaluate secondary endpoints using validated instruments as an additional indicator of benefit.

The M.D. Anderson Symptom Inventory-Brain Tumor Module (MDASI-BT or SP) allows the self-reporting of symptom severity and interference with daily activities. The MDASI-BT and Spine has demonstrated reliability and validity in the adult primary brain tumor patient population [25]. These tools represent a modification of the widely used and validated MDASI, with particular attention to symptoms common in patients with brain and spine tumors respectively. The availability of validated instruments provides an opportunity to prospectively assess the impact of treatment, both positive and negative, on patients. The evaluation of symptom burden in this study will assist in finding the best possible treatment with the least toxicity.

The MDASI-BT and/or MDASI-SP consists of symptoms rated on an 11-point scale (0 to 10) to indicate the presence and severity of the symptom, with 0 being "not present" and 10 being "as bad as you can imagine." Each symptom is rated at its worst in the last 24 hours. Symptoms included on the instrument include those commonly associated with cancer therapies, and those associated with the underlying disease. The questionnaire also includes ratings of how much symptoms interfered with different aspects of a patient's life in the last 24 hours. These interference items include: general activity, mood, work (includes both work outside the home and housework), relations with other people, walking, and enjoyment of life. The interference items are also measured on 0 - 10 scales.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Stage 1 Eligibility (Cohort 1 and 2)

- Cohort 1
  - Histologically confirmed by NCI Laboratory of Pathology intra-cranial or spinal **RELA-fusion** ependymoma of grade I, II or III.
  - Has received two or fewer prior chemotherapy regimens
- Cohort 2
  - Histologically confirmed by NCI Laboratory of Pathology intra-cranial or spinal **RELA-fusion** ependymoma of grade I, II or III.
  - Has received more than two prior chemotherapy regimens

2.1.1.2 Stage 2 Eligibility (Cohorts 3 and 4)

- Cohort 3
  - Histologically confirmed by NCI Laboratory of Pathology intra-cranial or spinal **non RELA-fusion** ependymoma of grade I, II or III.
  - Has received two or fewer prior chemotherapy regimens
- Cohort 4
  - Histologically confirmed by NCI Laboratory of Pathology intra-cranial or spinal **non RELA-fusion** ependymoma of grade I, II or III.
  - Has received more than two prior chemotherapy regimens

2.1.1.3 Patients must have an evidence of tumor progression as defined in Section **2.2.2.1**.

2.1.1.4 Patients must have had prior radiation therapy.

2.1.1.5 Patients must be ≥18 years old. Currently, no dosing or adverse event data is available on the use of marizomib in patients < 18 years of age; therefore only adults are included in this study. Patients < 18 years of age will be eligible for future pediatric trials.

2.1.1.6 Patients must have a Karnofsky performance status of ≥ 60 (see **Appendix A**).

2.1.1.7 Patients must have adequate organ and marrow function as defined below:

– leukocytes	≥3,000/µL
– absolute neutrophil count	≥1,500/µL
– platelets	≥100,000/µL
– hemoglobin	≥ 10 gm/dL (can be achieved by transfusion)
– AST(SGOT)/ALT(SGPT)	≤2.5 X institutional upper limit of normal
– Bilirubin	<1.5 mg/dL

- Creatinine up to 1.5-times upper institutional limits OR eGFR within normal as predicted by the CKD-EPI equation (≥ 60 mL/min/1.73m^2).
- Negative urine protein or urine protein concentration ≤ 60 mg/dL

2.1.1.8 The effects of marizomib on the developing human fetus are unknown. For this reason, 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 and up to 30 days after the last dose of the drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Anticancer treatment within designated period of time before enrollment including:

- surgery within 14 days
- needle or core biopsy within 7 days
- prior cytotoxic therapy within 28 days,
- vincristine within 14 days
- nitrosoureas within 42 days,
- procarbazine administration within 21 days
- non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid (radiosensitizer does not count) within 7 days; Avastin within 21 days. Any questions related to the definition of non-cytotoxic agents should be directed to the NCI Principal Investigator.

2.1.2.2 Treatment with any investigational agent within 28 days before enrollment.

2.1.2.3 History of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless patient is in complete remission and off all therapy for that disease for a minimum of 3 years.

2.1.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to marizomib.

2.1.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.6 Inadequately controlled hypertension (defined as systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg).

2.1.2.7 Current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per

investigator assessment).

2.1.2.8 New York Heart Association (NYHA) Grade II heart failure or greater or history of hospitalization for congestive heart failure diagnosis within 12 months prior to enrollment.

2.1.2.9 History of myocardial infarction or unstable angina within 3 months prior to enrollment.

2.1.2.10 A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >480 milliseconds (ms) (CTCAE grade 1) using Frederica's QT correction formula.

2.1.2.11 A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome).

2.1.2.12 Current use of concomitant medications that prolong the QT/QTc interval

2.1.2.13 History of stroke or transient ischemic attack within 3 months prior to enrollment.

2.1.2.14 Pregnant women are excluded from this study because marizomib's potential for teratogenic or abortifacient effects is unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with marizomib, breastfeeding should be discontinued if the mother is treated with marizomib.

2.1.2.15 Patients receiving combination antiretroviral therapy for treatment of Human Immunodeficiency Virus (HIV) or active anti-viral treatment for Hepatitis A, B or C infection. Anti-viral therapy, when combined with marizomib, poses a potential for pharmacokinetic interactions. Marizomib also increases immunosuppression, placing patients at an increased risk of acquiring lethal infections. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

2.1.3 Inclusion Criteria for Pregnancy Cohort (P)

Because the drug manufacturer would like to study the effect of the study therapy on pregnancy, and because the required information cannot be collected unless a subject is enrolled per ruling of the OGC, the following additional groups of subjects may be enrolled if necessary. The subjects enrolled in this cohort will not meet the inclusion and exclusion criteria found in **2.1.1** and **2.1.2.**

- A child whose parent (male or female) is/was an active participant in the study at any time during the child's gestation. Active participant is defined as having received at least one dose of study therapy through 6 months after the last dose of study therapy.

OR

- An expectant mother of child whose father is/was an active participant in the study at any time during the child's gestation. The father must have received at least one dose of study therapy. Active participant is defined as having received at least one dose of study therapy through 6 months after the last dose of study therapy.
- The expectant mother must be age 18 or older and must have the capacity to provide informed consent.

2.1.4 Recruitment Strategies

Participants will be recruited from the patient base who seek consultation for recurrent ependymoma or they may be pre-existing patients at NIH with ependymoma who have tumor progression. Ependymoma is a very rare disease entity with few treatment options and all attempts will be made to include under-represented minorities with ependymoma. This protocol may be abstracted into plain language announcements posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **12.8.3**.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol (01-C-0129 CCR Screeening protocol or 16-C-0151 NOB Natural History Protocol) within the timelines below may also be used to determine eligibility once a patient has signed the consent. The screening evaluation must be completed within 14 timelines noted in Section **2.4** unless otherwise noted:

2.2.2.1 Imaging

- MRI head and/or spine with gadolinium to confirm progressive disease. MRI parameters should follow the specifications detailed in **Appendix B.** If the steroid dose is increased between the date of imaging and consent, a new screening MRI is required after patient has been on a stable steroid dose for at least 5 days.
- Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease rather than radiation necrosis based upon either PET or Thallium scanning, MR spectroscopy, or surgical/pathological documentation of recurrent disease (Screening only).

2.2.3 History and physical examination

- Complete medical history and physical examination, including height, weight, vital signs, EKG, and Karnofsky performance status (**Appendix A)**
- Neurologic Exam (See **Appendix A**)

2.2.4 Laboratory Evaluation

- Hematological profile: CBC with differential and platelet count;
- Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, calcium,

phosphorus, albumin, magnesium, uric acid;

- Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy) (7 days prior to treatment registration);
- Urinalysis

2.2.5 Histologic confirmation

- Histologic confirmation of diagnosis and *RELA* fusion status by NCI Laboratory of Pathology (at any time point prior to treatment). If there is no available tissue samples, biopsy will be performed to confirm the diagnosis and *RELA* fusion status.

For baseline evaluations, please see section **2.4**

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Treatment Assignment Procedures (**For registration purposes only**):

Cohorts

Number	**Name**	**Description**
1	Cohort 1	Subjects with intra-cranial or spinal *RELA*-fusion ependymoma who have had none, 1 or 2 prior chemotherapies.
2	Cohort 2	Subjects with intra-cranial or spinal *RELA*-fusion ependymoma who have had more than 2 prior chemotherapies.
3	Cohort 3	Subjects with intra-cranial or spinal non *RELA*-fusion ependymoma who have had none, 1 or 2 prior chemotherapies.
4	Cohort 4	Subjects with intra-cranial or spinal non *RELA*-fusion ependymoma who have had more than 2 prior chemotherapies.
P	Cohort P	Children who may have been exposed to the study drug in utero OR expectant mothers of children who may have been exposed to the study drug in utero if mother not in a treatment cohort

Arm

Number	**Name**	**Description**
1	Arm 1	Marizomib at days 1, 8 and 15 of each 28-day cycle
P	Pregnancy evaluation	Data collection on pregnancy, birth and health of child up to 1 year.

Arm assignment

Subjects in Cohort 1, 2, 3 and 4 will be directly assigned to Arm 1.

Subjects in Cohort P will be directly assigned to Arm P.

2.4 BASELINE EVALUATION

Tests done at screening do not need to be repeated at baseline if performed in designated time frame prior to start of study drug.

Within 14 days prior to first dose:

- MRI of the head and/or spine with gadolinium as specified in **Appendix B**.
- Archived tumor samples will be collected to do molecular studies as described in Section **5.3.** If the patient has previously been on another study at NIH, and the required molecular profiling has been done, then additional pathology material may not be needed (any time prior to treatment initiation).
- The MDASI-BT and/or MDASI-SP . The choice of instrument will be based on the location of the index lesion for study enrollment. This may be in the brain (MDASI-BT), spine (MDASI-SP) or both (completing both instruments if lesions in the brain and spine are being followed for response). (For English speaking subjects only).
- Research blood for SNP Studies (See section **5.1.2**)
- Research blood for Pharmacogenomic Studies (Cohort 1 only) (See section **5.1.2**)
- Concomitant Medications
- Adverse events
- EKG (within 3 days prior to first dose)
- Subjects will complete and sign an NIH advanced directives form which is mandatory on this study.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 Cohorts 1-4:

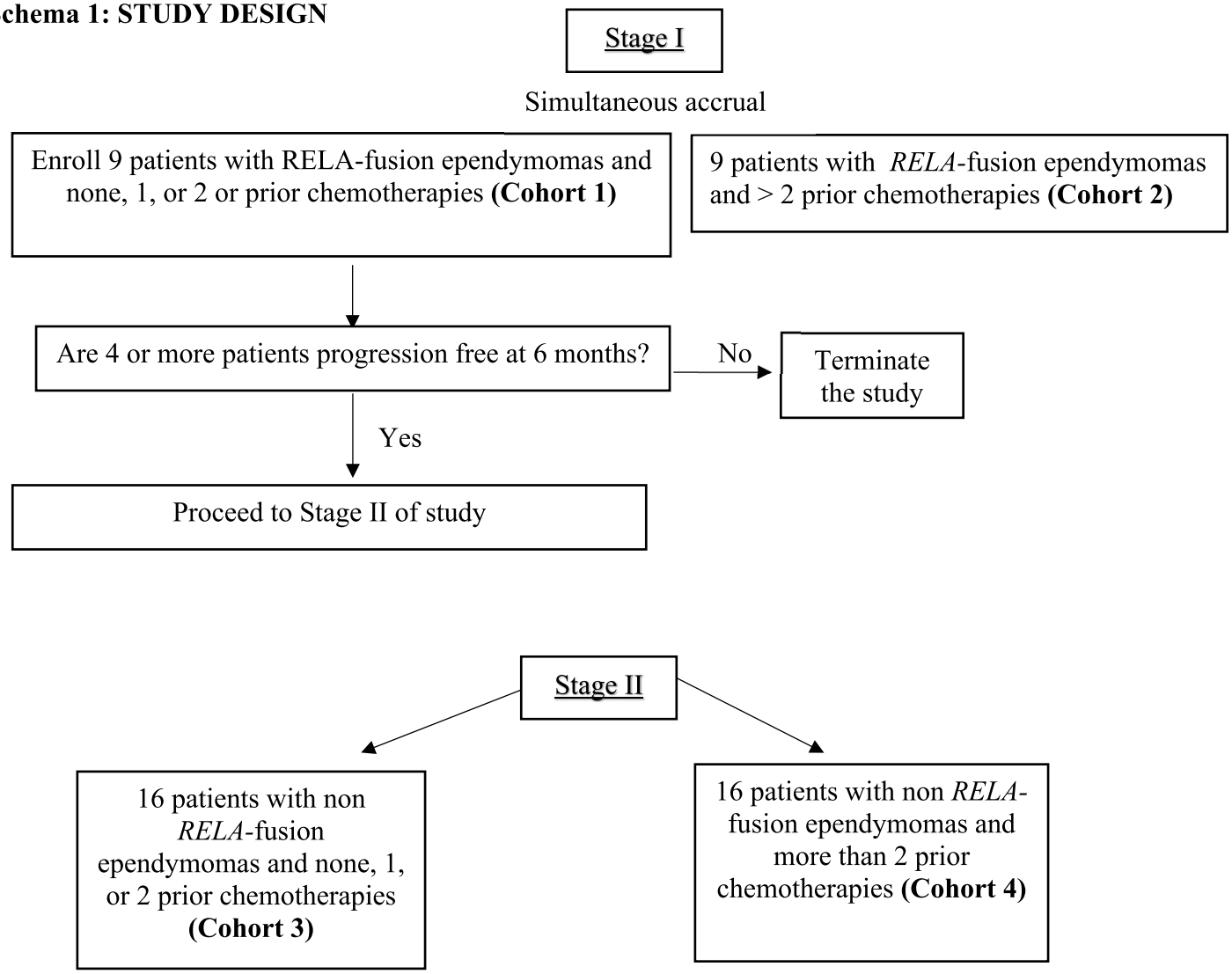
This is a phase II study to evaluate the efficacy of treatment with marizomib in *RELA*-fusion recurrent ependymoma and non *RELA*-fusion recurrent ependymoma. In the stage 1 of study, there will be simultaneous accrual into Cohorts 1 and 2. For Cohort 1, 9 patients with *RELA*-fusion ependymoma and none, 1, or 2 or prior chemotherapies will be enrolled.. For Cohort 2, 9 patients with RELA-fusion ependymomas and >2 prior chemotherapies. If we find evidence of clinical activity of marizomib, (4 or more patients in Cohort 1 are progression free at 6 months), we will proceed to stage 2, otherwise we will terminate the trial.

At stage 2, we will enroll patients into 2 cohorts:, 16 patients with non *RELA*-fusion ependymoma who had none, 1 or 2 prior chemotherapies (Cohort 3) and 16 patients with non *RELA*-fusion ependymoma who had more than 2 prior chemotherapies (Cohort 4).

During stage 2, enrollment into Cohorts 3 and 4 will occur simultaneously. Please see **Schema 1**.

One cycle is 4 weeks (+/- 3 days). Patients will be treated with IV marizomib at 0.8 mg/m^2 on days 1, 8 and 15 of each 28-day cycle until off treatment criteria are met (Section **3.8.1**).

Schema 1: STUDY DESIGN



3.1.2 Cohort P – Pregnancy Related Study Procedures, Birth and Health of Child

After signing the pregnant partner consent document, subjects in Cohort P, as well as women who may have become pregnant on any of the treatment cohorts will be asked to sign form NIH-1208, a request for release of medical information. Releases will be required for both the exposed child and for the expectant mother.

3.2 DRUG ADMINISTRATION

Marizomib will be administered at 0.8 mg/m^2 IV over at least 10 minutes (+10 minutes) (see section **14.1.5**).

Patients should be premedicated with ondansetron 8 mg IV or prochlorperazine 10 mg IV 60 minutes (+/- 30 minutes) prior to marizomib infusion to prevent nausea or vomiting.

The dose will be determined using the body surface area (BSA) calculated prior to each day 1 unless significant (> 3 kg) weight loss or gain is observed during a cycle. The BSA will be calculated from the height obtained at screening and the weight obtained at day 1 visit. The dose will be rounded to the nearest 0.1 mg.

On Cycle 1, Day 1, 8 and 15 vital signs will be taken within 10 minutes before the marizomib infusion and 10 (+/- 5) minutes, 30 (+/- 10) minutes, and 1 hour (+/- 15 minutes) following the marizomib infusion. For all subsequent cycles, vital signs will be assessed prior to the marizomib infusions and approximately 30 (+/- 10) minutes following each infusion.

Investigators should start assessing patients for CNS AEs (Section **8.1.6**) after the first marizomib dose, although frequently these AEs do not appear until Cycle 2 or later. Dose modifications guidelines for CNS adverse events are outlined in **Table 2**. A scale for rating severity of hallucinations is provided in **Appendix C.**.

Patients should be warned against driving or operating machinery if they develop CNS adverse events while receiving marizomib.

3.3 DOSE MODIFICATIONS

Dose modifications are explained in the **Table 2**, **Table 3** and **Table 4**
If the dose was reduced for AEs, there will be no dose re-escalation in subsequent treatment cycles.
After Dose level -3, no more dose reduction is allowed and patient will be taken off treatment.

Table 1: Marizomib Dose Reduction Levels

Dose Level	Weekly dose	Treatment Schedule
Starting dose	0.8 mg/m^2	Days 1, 8, and 15 (28-day cycle)
Dose level -1	0.7 mg/m^2	Days 1, 8, and 15 (28-day cycle)
Dose level - 2	0.55 mg/m^2	Days 1, 8, and 15 (28-day cycle)
Dose level - 3	0.4 mg/m^2	Days 1, 8, and 15 (28-day cycle)

Table 2: Marizomib Dose Modification Instructions

Marizomib-Related Adverse Event	Severity	Recommended Dose Modification
Central Nervous System		
Common CNS AEs including: ataxia, dizziness, gait disturbance, balance disorder, fall, dysarthria, confusion. For hallucinations management, please, see section **3.3.1**	Grade 1	Maintain current MRZ dose schedule without dose modification.
	Grade 2	Consider other supportive treatment (see **Table 4**); generally no dose-reductions are recommended. Consider dose-reduction if intolerable by patient due to interference with daily routine and/or if duration of event lasts longer than 3 days.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level. If AE has not resolved to ≤ Grade 1 (or baseline), skip the MRZ dose and resume with the next scheduled dose at reduced level (**Table 1**). In addition, consider other supportive treatment (see **Table 4**)
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). If re-challenge is an option, reduce MRZ dose level (**Table 1**). Treatment should be permanently discontinued if the toxicity does not resolve to grade 1 or less within 2 weeks.
Gastrointestinal		
Nausea, Vomiting	Grade 1 or 2	Implement prophylactic anti-emetic regimen according to local guidelines. Maintain current MRZ dose schedule without dose modification. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (**Table 1**) at the next scheduled MRZ dose administration.
	Grade 3 or 4	Implement prophylactic anti-emetic regimen according to local guidelines. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (**Table 1**) at the next scheduled MRZ dose administration. In addition, consider other supportive treatment (**Table 4**).

Marizomib-Related Adverse Event	Severity	Recommended Dose Modification
Other Adverse Events		
	Grade 2	Maintain current MRZ dose schedule without dose modification. Consider dose-reduction (**Table 1**) if intolerable by patient due to interference with daily routine and/or not resolved to ≤ Grade 1 (or baseline) at the next scheduled MRZ dose administration.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level (**Table 1**). If AE has not resolved to ≤ Grade 1 (or baseline), skip the MRZ dose and resume with the next scheduled dose at reduced level.
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). If re-challenge is an option, reduce MRZ dose level (**Table 1**). If toxicity continues beyond 2 weeks, consider permanent discontinuation.

3.3.1 Hallucinations management

Patients and care givers are warned about the possibility of hallucinations. Hallucinations are graded/characterized by the Lukoff criteria (Hallucination Severity Scale, **Appendix C**) and management guidelines based on these criteria are provided below in **Table 3**. Both therapeutic and prophylactic use of anti-psychotics may be considered for management of hallucinations. While there has been no correlation between medical history of mental illness and the incidence of hallucinations, patients with preexisting mental illness should be monitored closely and consideration given to prophylactic anti-psychotic dose increase.

Table 3: Hallucinations management:

	Recommended actions
Very Mild OR Mild OR Moderate	No marizomib dose reduction needed
Moderately severe, Related to marizomib	Stop marizomib until resolution to "Very Mild or Mild or Moderate" (or baseline). May use quetiapine fumarate or olanzapine as indicated. If hallucination resolves with treatment, consider continuing treatment and dosing on same schedule as before. If hallucination returns while on anti-psychotic, then dose reduction at the next dose (**Table 1**) is warranted.

	Recommended actions
Severe, Related to marizomib	At the next scheduled marizomib dose administration, dose-reduce one dose level (**Table 1**). If AE has not resolved to "Very Mild or Mild or Moderate" (or baseline), skip the marizomib dose and resume with the next scheduled dose at reduced level. In addition, consider other supportive treatment as per section (**Table 4**)
Extremely severe, Related to marizomib	Stop MRZ until resolution to "Very Mild or Mild or Moderate" (or baseline). If re-challenge is an option, reduce MRZ dose level (**Table 1**). Treatment should be permanently discontinued if the toxicity does not resolve to grade 1 or less within 2 weeks.

3.3.2 Marizomib Supportive Care

Subjects should receive premedication for nausea or vomiting and can receive other appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures are outlined below.

Table 4: Supportive Care Measures

Condition	**Supportive Care Measures**
Neutropenia or neutropenia with fever	Hematopoietic growth factors are permitted for grade 4 neutropenia or neutropenia with fever and should follow American Society of Clinical Oncology guidelines for their use. Prophylactic use of growth factors is not allowed, nor can they be used to improve blood counts to allow initiation of treatment.
Nausea, vomiting	The nausea and vomiting that may occur with marizomib administration can generally be managed through the use of appropriate supportive measures, anti-emetics (e.g., 5-HT3 antagonists, benzodiazepines, prochlorperazine). Patients should be premedicated with ondansetron or prochlorperazine 60 minutes (+/- 30 minutes) prior to marizomib administration.
Diarrhea	Specific guidelines for the use of loperamide for the subacute (days after administration) form of diarrhea are provided below: Patients should not be given drugs with laxative properties. Loperamide should be started at the earliest sign of: (1) a loose stool, or (2) the occurrence of 1-2 more bowel movements than usual in 1 day, or (3) a significant increase in stool volume or liquidity.

	Loperamide should be taken in the following manner: 4 mg at the onset of diarrhea and then 2 mg by mouth every 2 hours, around the clock until the patient is diarrhea free for at least 12 hours. Patients may take loperamide every 4 hours during the night. Patients should increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea.
CNS Events: Confusion, ataxia, delirium and any other neurological signs or symptoms	All Grades: When patients develop neurological symptoms during marizomib infusion, **stop the infusion**. Patients should be hydrated with 1 liter bolus of normal saline and should be observed for 2 hours. Brain imaging should be obtained as indicated. Educate patient not to drive and do not use heavy machinery until the neurological symptoms resolve. Grade 1 or 2 AE: Refer to **Table 2** Grade 2-3 AE: Follow guidelines for Grade 1-2 AE above, in addition; • Treat the AE with an appropriate medication if one is available. Some investigators have used quetiapine fumarate or olanzapine for hallucinations and methylphenidate for fatigue. • Dose modification as per **Table 1**.
Acute Kidney Injury	Hydrate with 1 liter bolus of normal saline.
Hypocalcemia	Calcium Supplements: Calcium supplements (e.g., calcium carbonate, 500 mg PO three times daily) may be required to maintain serum calcium levels above the lower limit of normal during chemotherapy treatment. Vitamin D supplements (e.g., ergocalciferol, 400 IU PO daily) may be appropriate for persistent hypocalcemia.

3.4 QUESTIONNAIRES

The MDASI-BT and/or MDASI-SP will be administered at baseline and at the time of imaging analysis. Every attempt should be made to administer the MDASI-BT and/or MDASI-SP prior to informing the patients about the results of the imaging study. The MDASI-BT or MDASI-SP will be completed only by the patient, unless changes in vision or weakness make this difficult. If this occurs, then the caregiver or research assistant may read the questions to the patient or assist with marking the severity number or score as described by the patient.

The average time to complete these instruments is 5 minutes. Only for English speaking patients.

3.5 FOLLOW UP

3.5.1 28-Day Safety Follow-up Visit

A Safety Follow-up visit is scheduled 4 weeks (28 ± 5 days) after the last administration of Marizomib but before any new therapy is started, if possible, whichever occurs earlier. The 28-Day Safety Follow-

up visit will comprise a full assessment for safety and tumor response as appropriate, which will include assessments indicated in Study Calendar, Section **3.6.**

3.5.2 Long-term Follow-up

All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up."

Subjects with progressive disease (PD) after the 28-Day Safety Follow-up visit, will be followed every 6 months (± 1 month) for survival (including assessment of any further anticancer therapy) by phone call or e-mail.

Subjects without PD at the 28-Day Safety Follow-up visit should continue follow up visits and tumor imaging by MRI as follows:

- every 2 months for 1 year after treatment stop date; then,
- every 3 months for 1 year; then,
- every 4 months for 1 year; then,
- every 6 months until progressive disease, lost to follow-up, or death.

3.6 STUDY CALENDAR

Procedure	**Screening**	**Baseline[1]**	**Cycles 1-24 (28+/-3 days) [1]**			**28 Days FU[11]**	**Long Term FU [10,11]**	
			Days[1]					
			1	**8**	**15**		**with PD**	**without PD**
Marizomib[2]			X	X	X			
NIH Advance Directives Form [3]		X						
Medical History	X							
Confirmation of Pathology	X							
Height	X							
Physical exam, neurological exam, KPS	X		X			X		X
Weight	X		X	X[12]	X[12]			
Vital signs	X		X[4]	X[4]	X[4]	X		X
EKG	X	X	X[13]	X[13]	X[13]			
CBC with differential	X		X[5]	X[5]	X[5]	X		
Biochemical profile [6]	X		X[5]	X[5]	X[5]	X		
Amylase / lipase/CK/ GGT, LDH			X[5]			X		
Urinalysis	X							
Serum or urine pregnancy test[7]	X		X[5]					
PT, INR, aPTT, fibrinogen			X			X		

Procedure	**Screening**	**Baseline**[1]	**Cycles 1-24 (28+/-3 days)** [1]			**28 Days FU**[11]	**Long Term FU** [10,11]	
			Days[1]					
			1	**8**	**15**		**with PD**	**without PD**
Tumor evaluation (MRI)[8]	X	X	X			X		X
Concomitant Medications (See **6.1**)		X	X	X	X	X		X
Adverse events (See **6.1**)		X	X	X	X	X		X
Research blood for SNP Studies		X						
Research blood for Pharmacogenomic Studies (Cohort 1 only)		X						
Collection of archival tumor sample for research studies		X						
MDASI-BT and/or MDASI-S[9]		X	X			X		X
Phone call or e-mail for survival/new cancer treatments							X	X

[1] Tests done at screening or baseline do not need to be repeated on baseline or Day 1 of Cycle 1 if performed in designated time frame prior to start of study drug. Time window +/- 3 days is allowed for Days 1, 8 and 15.

[2] 0.8 mg/m^2 IV.

[3] All subjects will complete and sign an NIH advanced directives form which is mandatory on this study.

[4] See section **3.2** for vital signs schedule on days of drug infusion.

[5] Labs will be obtained within 72 hours prior to dosing

[6] Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total bilirubin, calcium, phosphorus, albumin, magnesium, uric acid

[7] For women of child-bearing potential only

[8] MRI head and/or spine with gadolinium at screening/baseline and every 8 weeks after beginning of treatment. Confirmatory scans should also be obtained in 4-8 weeks period of time following initial documentation of objective response. Patients with prior therapy that included interstitial brachytherapy or stereotactic radiosurgery must have confirmation of true progressive disease at screening rather than radiation necrosis based upon either PET or Thallium scanning, MR spectroscopy, or surgical/pathological documentation of recurrent disease. After initial confirmation of progressive desease at screening, these patients will be evaluated during treatment with regular MRI.

[9] At baseline and then within 14 days prior to each imaging study.

[10] All SAEs ongoing at the 28-Day Safety Follow-up visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up." Subjects with PD after the 28-Day Safety Follow-up visit, will be followed every 6 months (± 1 month) for survival (including assessment of any further anticancer therapy) by phone call or e-mail.

Subjects without PD at the 28-Day Safety Follow-up visit should continue follow up visits and tumor imaging by MRI per schedule in the Section **3.5.2**

[11] If subjects are unable or not willing to come to NIH to for follow up visits, they will be followed by phone call or e-mail for survival, adverse events (for 1 year only) and further tumor therapy.

[12] If significant (> 3 kg) weight loss or gain is observed during a cycle.

[13] Within 2 hours after study drug infusion and additionally any time if clinically indicated.

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 28 days following the last dose of study therapy.

3.8.1 Criteria for Removal from Protocol Therapy

- Participant requests to be withdrawn from treatment (long-term follow up permitted)
- Progressive disease
- Unacceptable toxicity as defined in section **3.3**
- PI discretion
- Positive pregnancy test
- Completion of protocol therapy (24 cycles)

3.8.2 Off Study Criteria

- Death
- Patient becomes lost to follow-up
- PI discretion
- Participant requests to be withdrawn from the study

- Screen failure

3.8.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT MEDICATIONS / MEASURES

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. See also **Table 4**. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If medication changes occur during the trial period, documentation of drug dosage, frequency, route and date may also be included on the CRF.

Concomitant medications that prolong the QT/QTc interval are prohibited, excluding premedication required by protocol.

NOTE: Steroids: Steroid dosage will be carefully monitored and recorded during each course of therapy and steroid dosage changes will be considered before response determinations are made.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

This study will test for *RELA*-fusion in all study subjects. Not only is the presence of *RELA*-fusion a criterion for enrollment in the *RELA*-fusion ependymoma cohorts, it will also help us identify if the presence of this gene fusion is a predictive biomarker in treating ependymomas with a proteasome inhibitor.

In comparison to other gliomas, our understanding of the molecular characteristics of ependymomas is limited. Therefore, we will test the collected CNS tissue specimens for biomarkers (gene mutations, copy number alterations and fusions) using the neuro-oncology brain primary CNS panel as an exploratory analyses.

RNA sequencing on paraffin embedded or frozen tissue will be performed to study the expression of NF-κB pathway.

Blood specimens will also be collected at baseline for analysis of genetic variants including single nucleotide polymorphisms to help determine if there are genetic associations with the risk of developing CNS adverse events.

In Stage 1, Cohort 1, blood samples will be collected for pharmacogenetic studies to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET).

5.1.1 Tissue

In this study, archival tumor tissue will be collected from all patients and stored in the NIH Laboratory of Pathology (See section **5.2.2**).

5.1.2 Blood

Blood specimens will be collected at baseline to establish a genetic association with CNS adverse events and Pharmacogenomic Studies. Samples will be sent for barcoding and initial storage to Blood Processing Core (See section **5.2.1**)

Table 5: Tissue and blood specimen collected at baseline

Test/assay	**Volume blood**	**Type of tube/ tissue sample**	**Collection point**	**Location of specimen analysis**
NOB Brain Primary CNS panel		Archival tissue samples	Baseline	NIH Laboratory of Pathology
RELA fusion by IHC			Baseline	NIH Laboratory of Pathology
NF-κB pathway by RNA Sequencing			Baseline	NIH Laboratory of Pathology
Single nucleotide polymorphisms	Blood, 5 mL	EDTA (purple top) tubes	Baseline	NIH Laboratory of Pathology (Processed in Dr. Figg Lab)
Pharmacogenomic Studies by DMET Plus (Affymetrix)	Plasma, 6 mL	EDTA (purple top) tubes	Baseline (only Cohort 1)	Dr. Figg Lab

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through the Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH appropriate approvals and/or agreements, if required.

5.2.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.2.1.1 BPC contact information

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.2.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample bar-codes are linked to patient demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the LABrador. It is critical that the sample remains linked to patient information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.2.1.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB.

5.2.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissues are stored for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate

IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

Duplicate tissue samples, sample size permitting, will be banked for future analysis of RELA-fusion status in the event that preliminary results suggest that further development is warranted.

5.2.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any tumor tissue blocks or FFPE specimens that are remaining at the completion of the protocol will be stored at the Laboratory of Pathology at room temperature. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

If the patient withdraws consent the participants' data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 Description of the scope of genetic/genomic analysis

Genomic DNA and total RNA will be extracted from the FFPE tumor tissue sections mounted on slides, to enrich for viable tumor content, if indicated using the AllPrep DNA/RNA FFPE kit (Qiagen). The RNA will be reverse transcribed into complementary DNA (cDNA) using degenerate hexmer primer. An amplicon based sequencing library will be generated separately from the genomic DNA and cDNA by multiplex PCR using and AmpliSeq custom panel (ThermoFisher Scientific) of 869 PCR primer pairs (genomic DNA) and 69 primer pairs (cDNA) directed to detect small nucleotide variants in 52 genes, copy number in alterations in 21 genes, and fusions between 25 gene pairs that have been associated with cancer pathogenesis. RNA sequencing on paraffin embedded or frozen tissue will be performed to study the expression of NF-κB pathway. This genetic study will consist of somatic analysis on the tumor tissue.

Blood specimens will be collected for germline DNA analysis to establish a genetic association with CNS adverse events. DNA will be analyzed for Single nucleotide polymorphisms (SNP).

5.3.2 Pharmacogenomic Studies (Cohort 1 only)

One blood sample per patient will be collected from subjects enrolled in Cohort 1 for pharmacogenetic studies to analyze the genomic DNA and assess genotype of the most relevant drug metabolizing enzymes and transporters (DMET). DNA will be analyzed on a DMET Plus (Affymetrix) genotyping platform that tests for 1,936 genetic variations in 231 drug disposition genes, including 47 CYP (phase I metabolism) genes, 13 non-CYP (phase I metabolism) genes, 78 phase II metabolizing genes (including UGTs), 63 transporters, 4 genes involved in facilitation of drug transporters, 9 genes involved in global regulation of drug metabolizing/transporting proteins, 4 drug binding proteins, and 4 drug targets. The DMET data will be correlated with response and/or toxicity.

5.3.3 Privacy and Confidentiality of medical information/biological specimens

Study procedures and assessments will be done in private clinic rooms. Study related follow up calls will be done from a research office. Subjects will be encouraged to take the call from a private location (such as their home). Slides and tissue blocks will be stored in the Laboratory of Pathology (See section **5.2.2**).

Blood samples will be stored in the BPC (See section **5.2.1**) .

5.3.4 A Certificate of Confidentiality will be obtained for the study as described in section **12.6.8**.

5.3.5 Management of Results

Subjects will be contacted if a clinically actionable gene variant is discovered. Clinically actionable findings for the purpose of this study are defined as disorders appearing in the American College of Medical Genetics and Genomics recommendations for the return of incidental findings that is current at the time of primary analysis. (A list of current guidelines is maintained on the CCR intranet: https://ccrod.cancer.gov/confluence/display/CCRCRO/Incidental+Findings+Lists). Subjects will be contacted at this time with a request to provide a blood sample to be sent to a CLIA certified laboratory.

5.3.4 Genetic counseling

If the research findings are verified in the CLIA certified lab, the subject will be offered the opportunity to come to NIH (at our expense) to have genetic education and counseling with the NCI Genetics Branch to explain this result. If the subject does not want to come to NIH, a referral to a local genetic healthcare provider will be provided (at their expense). This is the only time during the course of the study that incidental findings will be returned. No interrogations regarding clinically actionable findings will be made after the primary analysis.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI or designee will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The MDASI-BT and/or MDASI-SP survey responses will be entered by study subjects electronically using the CCR Scribe system with data automatically uploaded directly into Labmatrix. The principal investigator, associate investigators/research nurses and/or a contract data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first study intervention, Study Day 1 through 28 days. Adverse events occurring more than 28 days after the last dose must only be recorded (and reported) if they are considered serious and at least possibly related to research interventions.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

All concomitant medications received within 28 days before the first dose of trial treatment and 28 days after the last dose should be recorded. Concomitant medications administered after 28 days after the last dose should be recorded for serious adverse events (SAEs) and events of clinical interest (ECIs) as defined in sections **8.1.2** and **8.1.6**.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Coded, linked or identified data with approved outside collaborators under appropriate agreements.

Data will be shared through*:*

- An NIH-funded or approved public repository: clinicaltrials.gov, dbGaP.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

Data will be shared:

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

The primary endpoint is progression-free survival at 6 months (PFS6). A combination of the neurological examination and MRI will be used to define progression. Due to improvements in neuroimaging and the

fact that tumor growth in certain regions of the CNS is without immediate neurologic signs and symptoms, greater reliance is placed on neuroimaging to define progression.

6.3.1 Disease Parameters

Measurable Disease: Bi-dimensionally measurable lesions with clearly defined margins by MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Based on RANO criteria **Table 6** [26].

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

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

6.3.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using an electronic measurement tool available through the imaging software. All baseline evaluations should be performed as closely as possible to the beginning of the treatment and never more than 2 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

6.3.3 RANO Disease Response Criteria

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. Confirmatory scans should also be obtained in 4-8 weeks period of time following initial documentation of objective response.

Table 6: RANO Criteria for Response

RANO Criteria for Response (28)				
	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥ 50% ↓	< 50% ↓ but < 25% ↑	≥ 25% ↑[1]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[1]
New lesion	None	None	None	Present[1]
Corticosteroids	None	Stable or ↓	Stable or ↓	n/a[†]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[1]
Requirement for response	All	All	All	Any[1]

RANO Criteria for Response (28)				
	CR	PR	SD	PD
[1] Progression occurs when this criterion is present †Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration. ↓ = decreased, ↑ = increased, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease. If PD is unclear based on white matter changes, patients may be kept on trial. FLAIR, fluid-attenuated inversion recovery; NA, not applicable.				

Stable/No Progression (SD): No evidence of new measurable lesions on MR imaging. The designation of Stable/No Progression requires a minimum of 12 weeks duration. All measurable and evaluable sites must be assessed using the same techniques as baseline.

Partial response (PR): ≥ 50% reduction in the sum of products of all measurable lesions over baseline sum observed using the same techniques as baseline. The patient must be on a stable or decreased dose of corticosteroids to be evaluable for response.

Complete response (CR): Complete resolution of all lesions. The patient cannot be on any corticosteroids with the exception of adrenal replacement doses.

Progression (PD): 25% increase in the sum of products of all measurable lesions over smallest sum observed (over baseline if no decrease) using the same techniques as baseline, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to death or deteriorating condition (unless clearly unrelated to this cancer).

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

NOTE: Steroids: Steroid dosage will be carefully monitored and recorded during each course of therapy and steroid dosage changes will be considered before response determinations are made.

6.3.4 Evaluation of Best Overall Response

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

6.3.5 Duration of Response

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

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

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

6.3.6 Progression-Free Survival

Progression-Free Survival: Progression free survival will be defined from the time of registration to the time of confirmed progression. In cases where this might be unclear, patients may continue on trial.

6.3.7 Overall survival

Overall survival: Defined as the time from registration to the time of death

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

The safety assessments will be performed according to the Study Calendar, Section **3.6**.

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (once a week) when patients are being actively treated on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Events of Clinical Interest (ECI) – CNS adverse events

Marizomib is known to cause CNS AEs (e.g., hallucinations - visual more common than auditory, confusion, mental status changes, delirium, etc.) ranging in severity from Grade 1 to Grade 4.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 Reporting of Serious Adverse Events

All SAE reporting must include the elements described in section **8.2.**

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Safety Reporting Criteria to the Pharmaceutical Collaborator

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

8.4.1 Serious Adverse Events

The Sponsor will report all serious adverse events to Celgene.

The Sponsor must inform Celgene in writing using a MEDWATCH 3500A or equivalent form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile or e-mail within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number MRZ-CL-BRAIN-NCI-12815 and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records. For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to marizomib based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene Corporation

Global Drug Safety and Risk Management

556 Morris Avenue, Building S12

Summit, New Jersey 07901

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8.4.2 Pregnancy

Any pregnancy occurring in either a female subject or partner of a male subject while in the treatment period, or within 28 days thereafter last dose, are considered immediately reportable events.

The Investigator will follow the female subject or partner of a male subject until completion of the pregnancy, and the Sponsor must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the CCR Pregnancy Report and Follow Up Form and CCR Pregnancy Outcome Form, Celgene Pregnancy Follow-up Report Form **Appendix D**, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to marizomib should also be reported to Celgene Drug Safety immediately by facsimile, or other

appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

8.4.3 Events of Clinical Interest (ECI): Hallucinations

Since hallucinations are an AE of interest, the type of hallucination, start and stop date, and severity are to be recorded in the CRF and a report provided to Celgene annually by the study team. See appendix **16.3**.

8.5 REPORTING PREGNANCY

8.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 28 days after the last dose of marizomib.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 28 days after the last dose should, if possible, be followed up and documented.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by an CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

The primary objective of this phase II study is to evaluate the efficacy of marizomib in *RELA*-fusion and non *RELA*-fusion ependymoma as measured by the primary endpoint of PFS6. Based on the preclinical data provided in Section **1.2.3** above, we postulate that the clinical activity of marizomib will be greatest in *RELA*-fusion supratentorial ependymoma, which has a constitutional activation of NF-κB pathway. If we see no PFS benefit with marizomib in *RELA*-fusion supratentorial ependymoma patients, then we do not expect that marizomib will benefit the non *RELA*-fusion ependymoma patients. To exploit such efficacy order of the two subgroups (RELA-fusion and non *RELA*-fusion), we employ a novel two-stage sequential enrichment design similar to Zang and Yuan (2016) [27]. In the first stage, we will enroll 18 patients with *RELA*-fusion ependymomas to test for clinical activity of marizomib. If 4 or more patients in Cohort 1 are progression free at 6 months, we proceed to stage 2; otherwise we terminate the trial and conclude that marizomib is not effective. Additionally, during stage 1, we will allow patients harboring RELA-fusion ependymoma with more extensive exposure to chemotherapy (> 2 chemotherapy regimens) to enroll. Given the preclinical data, this will enable this patient population to have access to a treatment regimen when most of the commonly used therapies have already been utilized. The responses of this group (Cohort 2) are a secondary objective and will not be used to make the determination of efficacy and will not be used for deciding to proceed to stage 2. However, the response results will be compiled as preliminary data regarding efficacy of marizomib as a salvage regimen for patients with heavily pretreated RELA-fusion ependymoma. At stage 2, we will enroll 16 patients with non *RELA*-fusion ependymomas (Cohort 3). Out of these 16 patients, if 9 or more patients are progression free at 6 months, we claim that marizomib is promising for treating both *RELA*-fusion and non *RELA*-fusion ependymoma; otherwise, we claim that marizomib is promising for treating *RELA*-fusion, but not for non *RELA*-fusion ependymoma. Based on historical data and clinical experience, we regard 30% of PFS6 as unpromising, and 60% of PFS6 as promising. The following table shows the operating characteristics of the above design based on 10,000 simulations.

Table 7. Operating characteristics of the two-stage sequential enrichment design

True PFS6 of *RELA*-fusion ependymomas	True PFS6 of	Probability of early stopping	Probability of claiming	Probability of claiming	Average sample size

	Non RELA-fusion ependymomas		effective for *RELA*-fusion	effective for all patients	
0.3	0.3	0.734	0.265	0.016	13.2
0.6	0.6	0.102	0.898	0.796	23.4
0.6	0.3	0.102	0.898	0.167	23.4
0.6	0.5	0.102	0.898	0.632	23.4

The study of salvage cohorts 2 and 4 is a secondary objective.

As patients in salvage cohorts 2 and 4 are highly heterogeneous, the efficacy of marizomib in *RELA*-fusion cohort 2 may not be notably higher than that in non *RELA*-fusion cohort 4. The objective of cohorts 2 and 4 is to estimate the efficacy of marizomib in recurrent ependymoma patients with multiple prior chemotherapies as measured by PFS6, PFS12, median PFS and OS. As a result, the 2-stage design will not be used for cohorts 2 and 4. Instead, we enroll patients into these cohorts simultaneously.

10.1.1 Primary Endpoint:

- Progression-free survival at 6 months of RELA-fusion and non RELA-fusion recurrent ependymoma patients treated with marizomib (Cohorts 1-4) will be assessed as proportion of patients that are progression-free at 6 months timepoint after initiation of treatment.

10.1.2 Secondary Endpoint(s):

- Progression-free survival at 12 months of RELA-fusion and non RELA-fusion recurrent ependymoma patients treated with marizomib (Cohorts 1-4) will be assessed as proportion of patients that are progression-free at 12 months timepoint after initiation of treatment
- Median progression-free survival (PFS) of RELA-fusion and non RELA-fusion recurrent ependymoma patients treated with marizomib (Cohorts 1-4) will be assessed as median amount of time subject survives without disease progression after initiation of treatment
- Overall survival (OS) of RELA-fusion and non RELA-fusion recurrent ependymoma patients treated with marizomib (Cohorts 1-4) will be assessed as median amount of time subject survives after initiation of therapy
- Progression-free survival at 6 months of RELA-fusion and non RELA-fusion recurrent ependymoma patients with with more than 2 prior chemotherapies treated with marizomib (Cohorts 2 and 4) will be assessed as proportion of patients that are progression-free at 6 months timepoint after initiation of treatment.
- Progression-free survival at 12 months of RELA-fusion and non RELA-fusion recurrent ependymoma patients with with more than 2 prior chemotherapies treated with marizomib (Cohorts 2 and 4) will be assessed as proportion of patients that are progression-free at 12 months timepoint after initiation of treatment
- Median progression-free survival (PFS) of RELA-fusion and non RELA-fusion recurrent ependymoma patients with with more than 2 prior chemotherapies treated with marizomib (Cohorts 2 and 4) will be assessed as median amount of time subject survives after initiation of therapy

- Overall survival (OS) of RELA-fusion and non RELA-fusion recurrent ependymoma patients patients with with more than 2 prior chemotherapies treated with marizomib (Cohorts 2 and 4) will be assessed as median amount of time subject survives after initiation of therapy
- Objective response to marizomib in RELA-fusion and non RELA-fusion recurrent ependymoma patients with with more than 2 prior chemotherapies treated with marizomib (Cohorts 2 and 4) will be assessed using RANO Criteria for Response **6.3.3**.
- Safety of marizomib in recurrent ependymoma patients and in a subset of patients with more than 2 prior chemotherapies (Cohorts 2 and 4) will be scored using CTCAE version 5.0.
- Outcome measures using self-reported symptom severity and interference with daily activities using the MDASI-BT and/or MDASI-SP instrument.

10.2 Sample Size Determination

To meet objectives of this study we need 50 patients. Considering screen failures, the total number of patients is set at 70 patients.

The sample size is calibrated and determined based on simulation to obtain desirable operating characteristics, as shown in **Table 7**. For example, when the treatment is effective (i.e., PFS6=0.6) for both RELA-fusion and Non RELA-fusion ependymomas, we have 0.796 chance to conclude that the treatment is effective for both types of ependymomas, and when the treatment is not effective (i.e., PFS6=0.3) for both RELA-fusion and Non RELA-fusion ependymomas, the probability of incorrectly claiming that the treatment effective is 0.016. Given the sample size of 9 (cohort 1), the 95% confidence interval of PFS6 is not wider than 0.32 on each side. Given the sample size of 16 (Stage 2 cohort 3), the 95% confidence interval of PFS6 and PFS12 is not wider than 0.24 on each side. The two salvage cohorts 2 and 4 are secondary and will not contribute to the statistical power of the study.

The anticipated accrual rate is 1 patient per month for *RELA*-fusion ependymoma cohorts and 1-2 patients per month for the non *RELA*-fusion ependymoma cohorts.

10.3 Populations For Analysis

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the Section **6.3.3**. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with Marizomib.

10.4 Statistical Analyses

10.4.1 Analysis of the Primary Endpoint:

Kaplan-Meier curve will be used to estimate the PFS6 for *RELA*-fusion and non *RELA*-fusion recurrent ependymoma. We will calculate mean, standard deviation and 95% confidence interval of PFS6. Logrank test and proportional hazard model will be used to compare the PFS between *RELA*-fusion and non *RELA*-fusion recurrent ependymoma.

10.4.2 Analysis of the Secondary Endpoint(s)

Kaplan-Meier curve will be used to estimate the PFS and OS for *RELA*-fusion and non *RELA*-fusion recurrent ependymoma with 2 or less prior chemotherapies, and *RELA*-fusion and non *RELA*-fusion recurrent ependymoma with more than 2 prior chemotherapies. Logrank test and proportional hazard model will be used to compare the PFS between *RELA*-fusion and non *RELA*-fusion recurrent ependymoma. Saftety will be assessed by reporting the grades of toxicity and the type of toxicity observed for all patients and summarizing data using the descriptive statistics, including mean, standard deviation and confidence intervals.

Received MDASI-BT or SP forms will be checked versus the timing schedule and considered as valid if they fall within ten days of the scheduled assessment. Compliance rates will be calculated as the number of received valid forms over the number of expected forms. Differences between groups in compliance will be tested by use of Fisher's exact test at every time point.

We will use descriptive statistics to describe how patients rate symptom severity and interference with function at each time point. Error bar graphs for each of the symptoms will be constructed at each time point. The proportion of patients rating their symptoms to be 7 or greater (on a 0-10 scale) will also be reported. We will construct individual patient profiles for each of the selected symptoms to describe the individual patients' patterns of change over time. We will calculate the mean core symptom severity, mean severity of the MDASI-BT or SP and mean symptom interference at the time of clinical evaluation. Estimates of differences in the mean symptom severity and mean symptom interference between responders and non-responders will be estimated in the intent to treat population. All patients with at least one valid questionnaire will be included in the analyses. In addition to the descriptive statistics, linear mixed model will be used to further study the trajectory of longitudinally evaluated patient reported outcome measures, where random intercepts will be used to capture the within-subject correlation.

Differences of at least 2 points will be classified as the minimum clinically meaningful change in the symptom severity and symptom interference measures. For example, an increase of 2 points or more would mean a moderate improvement, whereas a decrease of 2 points or more would be interpreted as moderate worsening. For individual symptoms, a rise in a symptom score means deterioration, whereas a reduced score means improvement of the specific symptom.

10.4.3 Safety Analyses

Saftety will be assessed by reporting the grades of toxicity and the type of toxicity observed for all patients and summarizing data using the descriptive statistics, including mean, standard deviation and confidence intervals.

10.4.4 Planned Interim Analyses

Two-stage sequential enrichment design will be used for this trial. In the first stage, we will enroll 9 patients with *RELA*-fusion ependymomas (Cohort 1) to test for clinical activity of marizomib. If 4 or more patients are progression free at 6 months, we proceed to stage 2; otherwise we terminate the trial and conclude that marizomib is not effective. At stage 2, we will enroll 32 patients with non *RELA*-fusion ependymomas (Cohort 3 and 4). From Cohort 3, if 9 or more of 16 patients are progression free at 6 months, we claim that marizomib is promising for treating both *RELA*-fusion and non *RELA*-fusion ependymoma; otherwise, we claim that marizomib is promising for treating *RELA*-fusion, but not for non *RELA*-fusion ependymoma. As above, PFS-6 for Cohort 4 will also be measured in patients with non-RELA fusion ependymoma that has been extensively treated. These data will be compiled as preliminary data regarding efficacy of marizomib as a salvage regimen for patients with heavily pretreated non-RELA-fusion ependymoma.

10.4.5 Exploratory Analyses

Determination of RELA gene fusion status and expression of NF-κB pathway to correlate with clinical course of ependymoma patients treated with Marizomib using Spearman correlation and regression analysis; the levels will be compared between responders and non-responders using an exact Wilcoxon rank sum test

Impact of baseline somatic genomic profile of ependymoma on clinical response to Marizomib. The number of somatic mutations, copy number alterations and fusions obtained for each patient will be compared between responders and non-responders. This will be done using either a Fisher's exact test, Cochran-Armitage trend test, or exact Wilcoxon rank sum test depending on the distributions of values.

Regression analysis will be further used to investigate the relationship between these covariates and clinical response.

Determination of single nucleotide polymorphisms from germline DNA to correlate with CNS adverse events will be established using an exact Wilcoxon rank sum tes.

11 COLLABORATIVE AGREEMENTS

11.1 CRADA

A CRADA (#03205) with Celgene is in place.

12 HUMAN SUBJECTS PROTECTIONS

12.1 Rationale For Subject Selection

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

12.2 Participation of Children/Viable Neonates

In this study, we are excluding the pediatric population (age <18 years) as no dosing or adverse event data are currently available on the use of marizomib in this group. Viable neonates/children may however be enrolled in Cohort P to study the effects of in utero exposure to the study drug. Data will be collected for up to 1 year after birth. These children may participate in the research under the provisions of 45 CRF Subpart D 46.404 as the research, consisting of data collection on health outcomes, is no more than minimal risk. There is no direct benefit to the child participants.

12.3 Participation Of Neonates Of Uncertain Viability And Nonviable Neonates

The assessments for this population on the study are limited to data collection, therefore no studies have been conducted for assessing potential risk as they would not be scientifically appropriate in this setting. No interventions are performed on the neonate and risks are limited to data breaches. Persons providing consent will be informed of these risks. Individuals engaged in the research will have no part in determining the viability of the neonate.

12.3.1 Neonates of Uncertain Viability

The purpose of the research, to collect data on the teratogenic effects of study drug exposure, is important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research as data breaches are a risk in the clinical setting as well. In addition,

consent from both parents will be obtained, unless exception criteria in the section **Consent for Children and Neonates** are met.

12.3.2 Nonviable Neonates

Vital functions of the neonate will not be artificially maintained as part of the research, nor will the research terminate the heartbeat or respiration of the neonate. The purpose of the research, to collect data on the teratogenic effects of study drug exposure, is important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research as data breaches are a risk in the clinical setting as well. In addition, consent from both parents will be obtained, unless exception criteria in the section **Consent for Children and Neonates** are met.

12.4 Participation of Pregnant Women

Pregnant women are excluded from enrolling in Cohorts 1-4 of the study due the possibly deleterious effects of the study drug. However, participants in cohort 1-4 who become pregnant may be retained on the study. In addition, the pregnant partners of male participants whose pregnancy occurred while during the male's participation in the study may be enrolled in Cohort P.

Pregnant women who were initially enrolled in Cohort 1-4 will be removed from study therapy to minimize the risk (Section **3.8.1**), but they will remain on follow up for safety with procedures limited to those that are generally permitted for pregnant women in the clinical setting. Data collection on the pregnancy represents no more than minimal risk, but it does not hold the prospect of direct benefit to the pregnant woman or to the fetus. However, the purpose of the data collection is the development of important biomedical knowledge that cannot be obtained by any other means. No inducements, monetary or otherwise, will be offered to terminate a pregnancy. No individuals engaged in the research will have any part in decisions as to the timing, method or procedures used to terminate a pregnancy and individuals engaged in the research will have no part in determining the viability of a neonate.

12.5 Participation of Subjects Unable to Give Consent

Adults unable to provide consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. For subjects that lose the ability to consent due to tumor progression, they will be taken off treatment but will have the opportunity to remain on study in long term follow-up for collection of outcomes for overall survival. If the reason for incapacity is due to a reason other than definitive disease progression and they are felt to be responding to the treatment under study in the opinion of the investigator, they will have the opportunity to continue this therapy.

All subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Please see section **12.8.1** for consent procedure.

12.6 Potential Risks/ Discomforts

12.6.1 Study Drug Risks

Marizomib may cause fatigue, dizziness, headache, insomnia, anorexia and gastrointestinal adverse effects. Patients may get cognitive changes, hallucinations and loss of balance which are generally reversible with dose reduction [20, 28]. Myelosuppression is uncommon [20, 28].

12.6.2 Imaging

Scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling. Participants undergoing gadolinium enhanced MRIs may also be at risk for kidney damage.

12.6.3 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.6.4 EKG

Other than the minor skin irritation from the electrodes there are no expected risks related to the EKG.

12.6.5 Other Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

12.6.6 Questionnaires risks

Questionnaires may contain questions that are sensitive in nature.

12.6.7 Non-Physical Risks of Genetic Research

12.6.7.1 Risk of receiving unwanted information

Anxiety and stress may arise as a result of the anticipation that unwanted information regarding disease related DNA sequencing or disease tendencies, or misattributed paternity. Patients will be clearly informed that the data related to DNA sequencing and genetic analysis is coded, investigational and will not be shared with patients, family members or health care providers.

12.6.7.2 Risk related to possibility that information may be released

This includes the risk that data related to genotype, DNA sequencing or risk for disease tendency or trait can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.6.8 Certificate of Confidentiality

As part of study efforts to provide confidentiality of subject information, this study will obtain a Certificate of Confidentiality which helps to prevent forced disclosure of personally identifiable research information. The Certificate of Confidentiality allows investigators on this trial to refuse to disclose identifying information related to the research participants, should such disclosure have adverse consequences for subjects or damage their financial standing, employability, insurability or reputation. The informed consent includes the appropriate coverage and restrictions of the Certificate of Confidentiality. his study may involve unpredictable risks to the participants.

12.6.9 Potential Benefits

The study drug may help to control the disease. Future patients may benefit from what is learned.

12.7 RISKS/BENEFITS ANALYSIS

This study is for patients who have relapsed from standard therapies for ependymoma. Currently, no

standard therapy at recurrence has been established, and the impact of chemotherapy at recurrence has been limited. Participants may obtain better responses with marizomib.

Please see section **12.2** above for the risk benefit analysis for children and viable neonates.

Please see section **12.3** above for the risk benefit analysis for nonviable neonates and neonates of uncertain viability.

Please see section **12.4** above for the risk benefit analysis for pregnant women.

12.8 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

12.8.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in Section **12.5**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.8**.

12.8.2 Consent for Children and Neonates

The consent procedures referenced above will be followed, with both parents involved in the consenting process per Sponsor request. The child's consent will be signed by both parents unless one parent is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. When guardianship status of the child is uncertain, documentation of custody status must be obtained.

As information is only collected for up to one year after birth, assent will not be obtained from child participants. While children may be enrolled after the age of 1 year for retroactive data collection if required, given the anticipated duration of the study, no child exposed in utero is expected to have attained the capacity to provide assent while the study is ongoing.

12.8.3 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH

Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the IC.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 MARIZOMIB (IND 139633)

14.1.1 Source

Marizomib is an investigational drug. The Center for Cancer Research (CCR), National Cancer Institute (NCI) will Sponsor the IND for this study. Marizomib will be supplied by the manufacturer (Celgene).

14.1.2 Human Toxicity

Refer to investigator brochure for detailed toxicity information.

14.1.3 Formulation and preparation

Marizomib Lyophile and Marizomib Lyophile Diluent are supplied in 2 vials as a kit placed in a single box that should be stored at 2ºC to 8ºC. Marizomib Lyophile and Marizomib Diluent are each provided in a 20-cc clear Type I glass vial with a Fluro-Tec® stopper and a Flip-off lid.

Marizomib Lyophile is supplied as a white to off white cake or powder of 2 mg marizomib and 60 mg sucrose per vial. Marizomib Lyophile Diluent is provided as a clear solution (20 mL) comprising 55% propylene glycol, 5% ethanol, and 40% citrate buffer (10 mM, pH 5).

Marizomib Lyophile vials are designated for single use only. For each subject treatment, 1 kit containing 1 vial of Marizomib Lyophile and 1 vial of Marizomib Diluent should be removed from the refrigerator. Do not warm the vials above 8°C.

The parenteral dosing solution of marizomib drug product from the lyophile formulation is prepared by removing 10 mL of Marizomib Diluent and adding it to the Marizomib Lyophile vial. (Note: Lyophile vials are sealed under vacuum and may pull syringed Diluent into the vial after needle insertion). Reconstitution should be performed under controlled, aseptic conditions. This results in a marizomib concentration of 0.2 mg/mL (2.0 mg in 10 mL/vial). The resulting reconstituted solution should be thoroughly mixed by vigorous shaking.

14.1.4 Stability and Storage

Marizomib Lyophile and Marizomib Diluent vials should be stored at 2°C to 8°C. The reconstituted marizomib solution should be thoroughly mixed by vigorous shaking and stored at 2ºC to 8ºC; the product should not be further diluted. The reconstituted MRZ dosing solution is stable in the dosing syringe for up to 2 hours in refrigerated conditions (2-8°C), AND up to an additional 1 hour when stored at Room Temperature (RT) conditions (20-25°C). A dosing syringe containing MRZ dosing solution removed from refrigeration and placed on an ambient surface will reach Room Temperature in approximately 10-15 minutes.

14.1.5 Administration procedures

Marizomib should be given as an intravenous infusion at 0.8 mg/m^2 over at least 10 minutes (+10 minutes)..

14.1.6 Incompatibilities

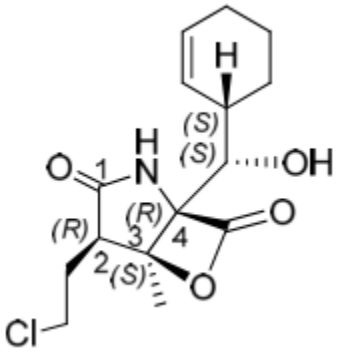
Marizomib is a second-generation irreversible proteasome inhibitor with a bicyclic β-lactone γ-lactam structure as below. Marizomib's lipophilic structure allows it to cross the blood-brain-barrier [16]. It inhibits the 20S proteasome, activates caspases and builds up reactive oxygen species to induce apoptosis in tumor cells [16].

14.1.7 Chemical name and structure:

(1R,4R,5S)-4-(2-chloroethyl)-1-((1S)-cyclohex-2-enyl(hydroxyl)methyl)-5-methyl-6-oxa-2-azabicyclo[3.2.0]heptane-3,7-dione

Formerly known as: 6-Oxa-2-azabicyclo[3.2.0]heptane-3,7-dione, 4-(2-chloroethyl)-1-[(S)-[(1S)-2-cyclohexen-1-yl]hydroxymethyl]-5-methyl-, (1R,4R,5S)

CAS Registry Number:	437742-34-2
Chemical class:	Bicyclic γ-lactam β-lactone
Other chemical identifier:	Salinosporamide A
Generic name:	Marizomib
Trade name:	Not assigned
Abbreviated name:	NPI-0052, MRZ
Molecular formula:	$C_{15}H_{20}ClNO_4$
Molecular weight:	313.78
Physical description:	White crystalline solid
Pharmacological class:	Proteasome inhibitor
Solubility in Organic solvents:	Isopropanol (5 mg/mL), ethanol (10 mg/mL), methanol (17 mg/mL), acetonitrile (13 mg/mL), propylene glycol (6 mg/mL), tert-butanol (2 mg/mL)
Solubility in Aqueous buffer:	5.5 µg/mL, pH 5



Chemical structure:
(Source: Ma, L and Diao, A et al. Anticancer Agents Med Chem. 2014 [18])

Marizomib appears to have a very low potential for drug: drug interactions as it is neither an inhibitor nor an inducer of hepatic CYPs from different species, it is not influenced by multiple drug resistant/ATP-binding cassette transporters and is inactive in a broad array of enzyme, ion channel, second messenger, and receptor assays.

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16 APPENDICES

16.1 APPENDIX A: KARNOFSKY PERFORMANCE STATUS AND NEUROLOGICAL FUNCTION

Patient's performance status and Neurologic Functions will be graded according to the following scales:

Karnofsky Performance Scale	
Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead.

Neurologic Function	
+2	Definitely Better
+1	Possibly Better
0	Unchanged
-1	Possibly Worse
-2	Definitely Worse
B	Baseline

Neurologic Function Score

This method of neurologic evaluation notes the presence or absence of neurologic symptoms. This examination should coincide with objective measurement in tumor size.

0 No neurologic symptoms
1 Minor neurologic symptoms
2 Moderate neurologic symptoms – fully active
3 Moderate neurologic symptoms – less than fully active
4 Severe neurologic symptoms

16.2 APPENDIX B: MRI ACQUISITION PROTOCOL

Acquisition protocol

- Auto-align scout (2 min)
- Pre-contrast T1 (2 min)
- High resolution T2 Volume (5 min)
- FLAIR (3 min)
- BOLD/ASL (*optional*) (14 min)
- Pre-contrast variable flip angle T1 maps (1 min)
- Permeability (T1 dynamic) (6 min)
- Post-contrast variable flip angle T1 maps (1 min)
- Diffusion Tensor Imaging (7 min)
- Perfusion (T2/T2*) (3 min)
- 3D Post-contrast (5 min)
- Post-contrast T1 (2 min)

Our proposed acquisition protocol is described in the box, and consists of approximately 65 minutes of imaging time (typically 90 to 120 minutes of time that the subject is in the magnet, counting setup and scan delays). Each of these datasets will be analyzed using tools that are published and well known in the neuroradiologic community. A brief outline of our analysis techniques follows:

Dynamic Contrast Enhanced – Magnetic Resonance Imaging (DCE-MRI)

DCE-MRI will be used to monitor the effects on tumor vasculature through parameters reflecting both tumor perfusion and permeability. This sequence uses a bolus injection of 0.1 mmol/kg of Gd-DTPA. Data will be analyzed using the standard Tofts/Kermode model with the typical approach of Patlak et al [21].

T2-weighted contrast-enhanced MRI or perfusion weighted imaging (PWI)

A second dose of Gd-DTPA (typically 0.1-0.2 mmol/kg) is administered for first-pass T2/T2-weighted imaging. We use a combination gradient-echo/spin echo approach to allow estimation of tumor vascular size based on the equations in the box. As shown in our earlier work [22], this can be used to estimate average vessel diameter, which we believe may change with effective anti-angiogenic therapy. This approach also provides estimates of cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and perfusion efficiency (1/MTT).

Diffusion Tensor Imaging (DTI)

We will measure the full water self-diffusion tensor before and after treatment in this patient population. The tensor fractional anisotropy (FA) will be calculated and can be used to define white matter tract directions and tumor invasion. Apparent diffusion coefficient (ADC) maps will also be calculated.

Simultaneous Blood Oxygenation Level Dependent (BOLD) and Arterial Spin Labeling (ASL) Imaging (Optional)

Combined BOLD/ASL imaging is a non-contrast approach to simultaneously measuring cerebral blood flow (ASL) and cerebral metabolic rate of oxygen consumption (BOLD) [31].

Our standard approach for this is to use a pulsed ASL sequence followed by a single-shot, gradient echo (GE) echo planar imaging acquisition. Two echoes are acquired, short echo (TE = 11 ms) for ASL (CBF maps) and longer echo (TE = 40 ms) for BOLD. Patients are administered room air and 100% oxygen at varying time points throughout the scan. The gas paradigm is as follows: baseline room air (8 min) – 100% O_2 (4 min) – washout room air (2 min) at a constant ~35 L/min flow rate. Blood oxygen levels are continuously monitored throughout the scan with a pulse oximeter.

16.3 APPENDIX C: HALLUCINATION SEVERITY SCALE

In addition to the adverse event (AE) data recorded for all AEs, an additional rating of the severity of hallucinations will be recorded in the CRF using the following criteria [32].

Since hallucinations are an AE of interest, the type of hallucination, start and stop date, and severity are to be recorded in the CRF.

Severity	Definition
Very mild	While resting or going to sleep, sees visions, smells odors or hears voices, sounds, or whispers in the absence of external stimulation, but no impairment in functioning.
Mild	While in a clear state of consciousness, hears a voice calling the individual's name, experiences non-verbal auditory hallucinations (e.g., sounds or whispers), formless visual hallucinations or has sensory experiences in the presence of a modality relevant stimulus (e.g., visual illusions) infrequently (e.g., 1-2 times per week) and with no functional impairment.
Moderate	Occasional verbal, visual, gustatory, olfactory or tactile hallucinations with no functional impairment OR non-verbal auditory hallucinations/visual illusions more than infrequently or with impairment.
Moderately Severe	Experiences daily hallucinations OR some areas of functioning are disrupted by hallucinations.
Severe	Experiences verbal or visual hallucinations several times a day OR many areas of functioning are disrupted by these hallucinations.
Extremely Severe	Persistent verbal or visual hallucinations throughout the day OR most areas of functioning are disrupted by these hallucinations.

16.4 APPENDIX D: CELGENE INITIAL PREGNANCY REPORT FORM

Pregnancy Form Completion Guidelines
For Initial and Follow-up Reports

General Instructions

Any pregnancy that occurs during a clinical study with an investigational drug will be reported for **tracking purposes only**. **Pregnancy complications and abnormal outcomes must be reported as Adverse Events (AEs). If a pregnancy complication or abnormal outcome meets any of the serious criteria, it must be reported as a Serious Adverse Event (SAE) to Celgene Drug Safety using the SAE Report Form.**
All pregnancies and suspected pregnancies (e.g., reports of elevated, questionable or indeterminate beta human chorionic gonadotropins in females of child bearing potential or positive urine pregnancy test) of female subjects or female partners of male subjects (and exposures of other pregnant females if required by protocol) that occur during the period defined in the protocol must be reported to Celgene Drug Safety **immediately** using the Pregnancy Initial Report Form. All such pregnancies and suspected pregnancies occurring during the study will be followed until delivery or other outcome, if possible. The outcome must be reported to Celgene Drug Safety **immediately** using the Pregnancy Follow-up Report Form.
The Initial report will be completed with initial pregnancy data. The Follow-up report will be completed with ongoing pregnancy data and/or pregnancy outcome data.
The Header and Demographic Information, and Study Drug Information should be completed based on the study subject. All other information, e.g., Concomitant Medications, Diagnostic Tests, Complications and other pregnancy information should pertain to the pregnant female.
Each Pregnancy form must be completed in English. Please print or type all entries in blue or black ink.
Dates should be entered in dd/mmm/yyyy format (e.g., August 21, 2009 = 21/AUG/2009).
Provide all available information at the time of form completion. If any information is unknown, enter "UNK" in the space provided rather than leaving it blank.
Fax the completed Pregnancy Reporting form(s) to the appropriate Celgene Drug Safety local office corresponding to your country as per the directory found at the end of this document. Retain a copy of the successful fax transmission report along with the pregnancy form in your study file. If your fax machine does not provide a transmission report, annotate the pregnancy form with the date and time it was faxed to Celgene. You may also email the pregnancy form to the Celgene Drug Safety local office email provided at the end of this document. Please print a copy of the sent email for your files. All emailed forms still ultimately require the Investigator's signature.

Completion of Pregnancy Initial Report Form

Header and Demographic Information	• Enter the Protocol Number in the space provided • Record the date the site first became aware of the pregnancy, suspected pregnancy or exposure • Record the name of the Principal Investigator at the site • Record the subject initials as recorded in the Case Report Form • Record the 3-digit site number assigned to the study site • Record the 4-digit subject number that was assigned to the subject • Record the subject's age at the time of the pregnancy • Record the sex of the study subject, regardless of whether the pregnant female is the study subject or not • Record the type of pregnancy being reported, i.e., pregnancy of a female subject, pregnancy of a female partner of a male subject, suspected pregnancy or exposure of a pregnant female • Record subject's race; check one box, unless the race is not listed then check other and specify
Pregnancy Information	• For female subjects only, record the date of the Screening pregnancy test using the following format: dd/mmm/yyyy, and check the corresponding result box • Record the date of the last menstrual period using the following format: dd/mmm/yyyy • Record the total number of prior pregnancies • Record the number of prior live births • Record the number of terminated pregnancies (spontaneous or elective) • Record history of congenital anomalies with prior pregnancies by checking the appropriate box • Record history of familial congenital anomalies by checking the appropriate box
Concomitant Medication Information	• Include all medications taken at the time of study entry, during study treatment, and at the time of conception (additional pages can be attached as necessary)
Study Drug Information	• Record the study drug name received by the study subject or indicate blinded treatment as appropriate • Record the date of first dose and the date of the last dose using the following format: dd/mmm/yyyy
Method of Birth Control Information	• Record all methods in use since starting study drug

Pregnancy Diagnosis Information	• Record the type of pregnancy test initially used • Provide the date pregnancy test was performed using the following format: dd/mmm/yyyy
Pregnancy Status Information	• Record the number of weeks the female is pregnant OR check "No longer Pregnant" if the pregnancy has ended (if no longer pregnant, complete a Pregnancy Follow-up Report) • Indicate whether the female plans to carry the pregnancy to term or plans to terminate the pregnancy • If the female plans to carry to term, provide the expected date of delivery using the following format: dd/mmm/yyyy • Provide the date of pregnancy termination or circle "Pending" if date is not known
Summary of Diagnostic Tests Information	• Indicate if any diagnostic tests were performed by checking "None" or listing the tests and their results as appropriate • Do not include pregnancy test information here
Pregnancy Complication Information	• Indicate if any pregnancy complications have occurred by checking "None" or summarizing the complications as appropriate
Form Completion Information	• Print the name of the Investigator and obtain the Investigator's signature • Record the date (dd/mmm/yyyy) the Investigator signed the report • Print the name of the reporter, include the reporter's signature • Record the date (dd/mmm/yyyy) the reporter signed the report • Document the reporter's phone number, fax number and email address

Completion of Pregnancy Follow-up Report Form

If the outcome of the pregnancy is abnormal (e.g., spontaneous abortion [any congenital anomaly detected in an aborted fetus must be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the Investigator must report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety using the SAE Report Form.	
Header and Demographic Information	• Enter the Protocol Number in the space provided • Record the date the site first became aware of the pregnancy, suspected pregnancy or exposure • Record the name of the Principal Investigator at the site • Record the subject initials as recorded in the Case Report Form • Record the 3-digit site number assigned to the study site • Record the 4-digit subject number that was assigned to the subject • Record the subject's age at the time of the pregnancy • Record the sex of the study subject, regardless of whether the pregnant female is the study subject or not • Record subject's race; check one box, unless the race is not listed then check other and specify
Summary of Diagnostic Tests Information	• Indicate if any diagnostic tests were performed since the initial report by checking "None" or listing the tests and their results as appropriate
Pregnancy Complication Information	• Indicate if any pregnancy complications have occurred since the initial report by checking "None" or summarizing the complications as appropriate
Ongoing Pregnancy Status OR Outcome Information	• Record the number of weeks the female is pregnant OR • Check the applicable outcome • Provide the date of delivery or termination using the following format: dd/mmm/yyyy • Provide the birth weight • Indicate the method of delivery by checking the appropriate box • Provide the gestational age at delivery • Provide the respective APGAR scores at 1, 5 and/or 10 minutes
Comments Section	• Record any additional information not already provided including: changes in concomitant medications since previous report and medications at delivery, complications after delivery or discovery of an anomaly

Form Completion Information	• Print the name of the Investigator and obtain the Investigator's signature • Record the date (dd/mmm/yyyy) the Investigator signed the report • Print the name of the reporter, include the reporter's signature • Record the date (dd/mmm/yyyy) the reporter signed the report • Document the reporter's phone number, fax number and email address

Page 1 of 1

Celgene

PREGNANCY INITIAL REPORT

Pregnancy reports must be sent to Celgene Drug Safety IMMEDIATELY

Protocol No.: MRZ-CL-BRAIN-NCI-12815

Date site first became aware of Pregnancy: dd mon yyyy

Investigator Name: _____

Subject Initials (F, M, L): _____ **Site No.:** _____ **Subject No.:** _____ **Subject's Age:** _____

Sex of Subject: ☐ **Female** ☐ **Male**

☐ **Pregnancy of Subject** ☐ **Pregnancy of Subject's Partner**

☐ **Suspected Pregnancy** ☐ **Exposure of a Pregnant Female**

Race: ☐ Black ☐ White ☐ Asian

☐ Other, specify _____

Screening Pregnancy Test: dd mon yyyy

Negative? ☐ Yes ☐ No

Last Menstrual Period: dd mon yyyy

Total # prior pregnancies: _____

Total # prior live births: _____

Total # terminations (spontaneous and elective): _____

History of congential anomalies with prior pregnancies? ☐ Yes ☐ No

History of familial congential anomalies? ☐ Yes ☐ No

Concomitant Medications: (at time of study entry, during study treatment and at conception) Attach additional sheets as necessary

Study Drug Name: _____

Date of First Dose: dd mon yyyy

Date of Last Dose: dd mon yyyy

Method of Birth Control: **(Check (√) all that apply)**

☐ Abstinence
☐ Condom
☐ Diaphragm
☐ Depo Contraceptive (e.g., Norplant, Depo-Provera)
☐ Intrauterine Device (IUD)
☐ Oral Contraceptive
☐ Rhythm Method
☐ Spermicide
☐ Sterilization (female)
☐ Sterilization (male)
☐ None
☐ Other: _____

Pregnancy Initially Diagnosed By: ☐ Home Urine Test ☐ Office Urine Test ☐ Serum Test

Date of Pregnancy Test: dd mon yyyy

Female is Currently: _____ weeks pregnant OR ☐ No longer Pregnant (If no longer pregnant, complete Pregnancy Follow-up Report)

Female has Elected to: ☐ Carry Pregnancy to Term (Expected Date of Delivery):

☐ Terminate Pregnancy (Date Performed or Pending): dd mon yyyy

Summarize Diagnostic Tests to Date (e.g., ultrasound, amniocentesis): ☐ None

Describe Complications with Pregnancy to Date

☐ None

Investigator's Name and Signature: _____ **Date:** dd mon yyyy

Reporter's Name and Signature: _____ **Date:** dd mon yyyy

Reporter's Phone Number: _____ **Reporter's Fax Number:** _____ **Reporter's E-mail Address:** _____

NOTE: Please use the first three letters of the month (e.g.: JAN)

INIT PREG Form 26 May 2010

Celgene

PREGNANCY FOLLOW-UP REPORT

Pregnancy reports must be sent to Celgene Drug Safety IMMEDIATELY

Protocol No.: MRZ-CL-BRAIN-NCI-12815

Date site first became aware of Pregnancy: ____ ____ ____ (dd mon yyyy)

Investigator Name: _____

Subject Initials (F, M, L): ____ **Site No.:** ____ **Subject No.:** ____ **Subject's Age:** ____

Sex of Subject: ☐ Female ☐ Male

Race: ☐ Black ☐ White ☐ Asian ☐ Other, specify _____

Summarize Diagnostic Tests to Date
(e.g., ultrasound, amniocentesis): ☐ None

Describe Complications with Pregnancy to Date
☐ None

If a pregnancy complication or abnormal outcome meets serious adverse event reporting criteria, an SAE form should be completed and faxed to Celgene Drug Safety IMMEDIATELY.

Female is Currently: _____ weeks pregnant OR

Date of Delivery/Termination: ____ ____ ____ (dd mon yyyy)

Birth Weight: _____

Method of Delivery:
☐ Vaginal ☐ C-section ☐ Forceps/Vacuum extraction

Gestational Age at Delivery: _____

Apgar Score: _____ 1 min. _____ 5 min. _____ 10 min.

Pregnancy Outcome
- ☐ Elective Termination, specify in Comments
- ☐ Premature birth/congenital anomaly *
- ☐ Premature birth/healthy infant
- ☐ Term birth/congenital anomaly *
- ☐ Term birth/healthy infant
- ☐ Spontaneous abortion
- ☐ Stillbirth
- ☐ Unknown/Lost to follow-up

** If anomaly, please provide comments below*

Comments: (Include changes in Concomitant Medications since previous report and medications at delivery, e.g., epidural)

Investigator's Name and Signature: **Date:** ____ ____ ____ (dd mon yyyy)

Reporter's Name and Signature: **Date:** ____ ____ ____ (dd mon yyyy)

Reporter's Phone Number: **Reporter's Fax Number:** **Reporter's E-mail Address:**

NOTE: Please use the first three letters of the month (e.g.: JAN)

FOLLOW-UP PREG Form 26 May 2010