STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: PHASE II STUDY OF EVEROLIMUS (RAD001, AFINITOR®) FOR CHILDREN WITH RECURRENT OR PROGRESSIVE EPENDYMOMA

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PHASE II STUDY OF EVEROLIMUS (RAD001, AFINITOR®) FOR CHILDREN WITH RECURRENT OR PROGRESSIVE EPENDYMOMA

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Signature Page
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The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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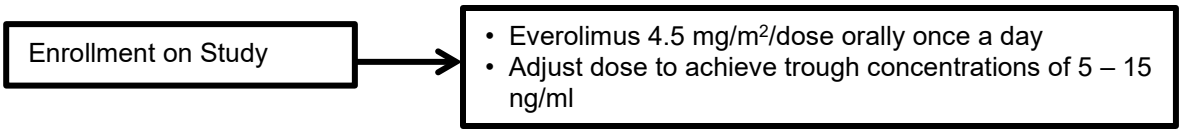
LIST OF ABBREVIATIONS

Examples Include:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&P	History & Physical Exam
HRPP	Human Research Protections Program
INR	International Normalized Ratio
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase II Study of Everolimus (RAD001, Afinitor®) for Children with Recurrent or Progressive Ependymoma
Short Title	Everolimus (RAD001, Afinitor®) for Children with Recurrent or Progressive Ependymoma
Protocol Number	CRAD001CUS224T
Phase	Phase II
Methodology	Single Arm, Open Labeled Clinical Trial
Study Duration	5 years
Study Center(s)	UT Southwestern Medical Center and approved subsites.
Objectives	• Determine the Objective Response Rate (ORR = Complete Response Rate + Partial Response Rate + Prolonged Stable Disease Rate) following treatment with everolimus for children with recurrent or progressive ependymomas. • Determine the duration of response, progression free survival (PFS) and event free survival (EFS) following treatment with everolimus for children with recurrent or progressive ependymomas. • Determine safety and tolerability of everolimus among children with recurrent or progressive ependymomas. • Descriptive analysis and correlation of response rate to biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated PRAS40 (pT246), phosphorylated 4EBP1, phosphorylated $P70^{S6K}$, and PTEN expression.
Number of Subjects	18 Patients
Diagnosis and Main Inclusion Criteria	Recurrent or Progressive Ependymoma
Study Product(s), Dose, Route, Regimen	Everolimus (RAD001, Afinitor®) orally once a day.
Duration of administration	Up to 2 years.
Reference therapy	None
Statistical Methodology	Objective response rate and the corresponding 95% confidence interval will be estimated using the exact binomial method. Kaplan-Meier method will be used to estimate the duration of response, progression free survival (PFS) and event free survival (EFS). Exploratory analysis will be conducted for correlative studies.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Recurrent Ependymoma: Ependymoma is the third most common central nervous system neoplasm in children, accounting for approximately 10% of childhood brain tumors.[1] Although the prognosis for children with newly-diagnosed completely resected ependymomas is often good,[2-5] children with incompletely resected tumors often suffer repeated episodes of tumor progression and die as a result of their tumor.[6-8] The prognosis for children with recurrent or progressive ependymomas is especially dismal and the majority of children with recurrent or progressive ependymomas will eventually succumb to their tumor within 8.7 to 24 months.[9,10] At the time of tumor recurrence, therapeutic options are limited. A recent report by Merchant and co-workers described several long-term survivors after tumor recurrence when treated with a second course of radiation therapy.[11] Unfortunately, although chemotherapy occasionally demonstrates anti-tumor activity against recurrent ependymoma, responses are rarely durable.[12] Indeed, a recent review by Bouffet and co-workers concluded that the frequency of durable responses of recurrent ependymomas to chemotherapy was disappointing and encouraged a re-evaluation of the current chemotherapeutic approach to intracranial ependymoma and that studies are needed to identify new biological targets to inform future clinical trials.[9]

1.2 Everolimus: Background and Associated Known Toxicities

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Everolimus was developed in oncology as Afinitor® and was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TS. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of adult patients with tuberous sclerosis complex (TSC) who have renal angiomyolipoma not requiring immediate surgery.

Approximately 30,582 cancer patients have been treated with everolimus as of September 30, 2013:

- 16,671 patients in Novartis-sponsored clinical trials
- 1,911 patients in the individual patient supply program
- > 12,000 patients in investigator-sponsored studies.

The following is a brief summary of the main characteristics of Everolimus. More complete information can be obtained from the Everolimus Investigator's Brochure (IB).

Overview of Everolimus: Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers.13

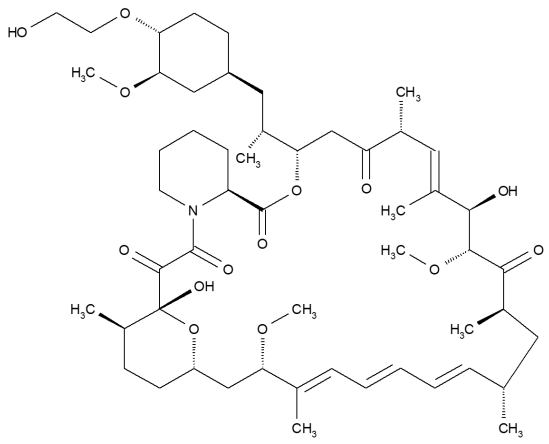
Everolimus is being investigated as an anticancer agent based on its potential to act:

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Table 1-1 Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-[(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1 Chemical structure of Everolimus



mTOR Pathway and Cancer: At the cellular and molecular level, Everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development.[14]

The main known functions of mTOR include the following:[15]

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels;
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers;[16,17]
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers;[18]
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

Non-clinical experience: Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to µM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that Everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of Everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of Everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of Everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to Everolimus *in vitro*.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and “relatively resistant” *in vitro*. In general, Everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to Everolimus. Molecular analysis has revealed that relative sensitivity to Everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of Everolimus in experimental animal tumor models showed that Everolimus monotherapy typically reduced tumor cell growth

rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

All significant adverse events observed in toxicology studies with Everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

Further details can be found in the Everolimus Investigator's Brochure.

1.3 Rationale

The purpose of this study is to evaluate the anti-tumor activity of Everolimus among children with recurrent or progressive ependymoma. The rationale for this study is based upon both pre-clinical and clinical considerations. Recurrent or progressive ependymoma is incurable and has very limited treatment options. In 2011, our group published a case report describing a young child with a multiply recurrent ependymoma after 4 chemotherapy regimens and several courses of radiation therapy and who had an objective and long lasting response to sirolimus (Rapamune, Pfizer).[19] This patient, who had been treated with various regimens over a span of 20 months without response, subsequently had a near complete response to sirolimus of 18 months duration. Subsequently, a second child with a recurrent ependymoma was treated with sirolimus and oral etoposide and had a near-complete response of 18 months duration. Furthermore, immunohistochemistry studies have revealed that 20 out of 23 (87%) pediatric ependymomas were immunoreactive for phosphorylated S6, a biomarker that often predicts response to mTOR pathway-targeted therapy.[20,21] Finally, a study from Rogers and co-workers identified P-AKT protein expression, indicating PI3K-mTOR pathway activation, was present in 72% of 169 pediatric ependymomas tumors.[22] P-AKT expression was found to be an independent marker of a poorer progression-free survival. A significant association between PI3K pathway activation and cell proliferation was identified, suggesting that pathway activation was influencing this process. They concluded that PI3K-mTOR pathway activation could be a biomarker and potential therapeutic target for pediatric ependymomas.

Existing data regarding the anti-tumor activity of mTOR inhibitors among children has demonstrated that mTOR inhibitors are well tolerated and have activity against pediatric brain tumors. For example, Franz et al. reported five children with tuberous sclerosis complex and progressive subependymal giant cell astrocytomas who were treated with sirolimus to achieve target trough concentrations between 5 – 15 ng/mL.[23] All tumors demonstrated objective responses to sirolimus. One patient who interrupted sirolimus therapy experienced tumor progression that responded to resumption of sirolimus therapy. A subsequent phase III study of everolimus compared responses of 78 patients treated with everolimus versus 39 patients treated with placebo. 27 of 78 (35%) patients in the everolimus group had at least 50% reduction in the volume of subependymal giant cell astrocytomas versus none in the placebo group ($p<0.0001$). Adverse events were mostly grade 1 or 2 and no patients discontinued treatment because of adverse events. [24] A phase I study of everolimus by Fouladi et al. evaluated everolimus at doses between 3 - 6.5 mg/m^2/day.[25] No children in this study had objective tumor responses, 6 of 18 children who were assessable for response had stable disease for 4 to 14 months. In this study there were 4 children with ependymomas, one who had prolonged stable disease and three other who had progressive disease. Of the 25 children with a variety of different pediatric cancers

enrolled on this study, tumors from 13 of 14 patients demonstrated immunoreactivity against phosphorylated S6 [average of 33%; range = 10% - 90%)]. In this study, no relationship was observed between the level of phosphorylated S6 immunoreactivity in pretreatment tumor samples and patients' tumor response.

The poor in vivo and in vitro response of a single ependymoma cell line to sirolimus in a study from the Pediatric Preclinical Testing Program[26] and the heterogeneity observed in ependymoma response in the phase I study of everolimus in children Fouladi et al.[25] may be explained by differential activation of mTORC1 in tumors. Indeed, our analysis of phosphorylated S6 is consistent with this notion. S6 is a protein of the small ribosomal subunit that is phosphorylated by S6 kinase 1 (S6K1) and 2 (S6K2), which in turn are regulated by mTORC1, and while S6K is regulated by kinases other than mTORC1, phosphorylated S6 tends to correlate with mTORC1 activation and phospho-S6 appears to be associated with tumor sensitivity to mTORC1 inhibitors.[27-30] In our series of eleven cases of Grade II infratentorial ependymomas, 7 cases showed phosphorylated S6 but 4 did not. Since it would be expected that only those tumors with active mTORC1 would respond to mTORC1 inhibitors, and this was the case in our two patients, it would be fitting that clinical trials examining the role of mTORC1 inhibitors for this disease would evaluate patients in which there was evidence of mTORC1 activation in the tumor.

1.4 Rational for Targeted Dose

A concern regarding the use of Everolimus in oncology is the potential for immunosuppression during treatment. Consequently, in addition to individualizing the Everolimus dose according to the patient's body surface area, this protocol requires the upward titration of the dose from 4.5 mg/m^2, subject to tolerability, with the objective of achieving trough Everolimus levels in the range of 5-15 ng/mL. This range is based on the Phase II data from a TSC study conducted at the Cincinnati Children's Hospital Medical Center.[24] In this study, patients were treated with Everolimus from a starting dose of 3 mg/m2 with subsequent upward titration to attain a RAD001 trough in the range 5-15 ng/mL. This regimen was efficacious (35% of patients had >50% shrinkage at 6 months) and showed acceptable tolerability. The starting dose of 4.5 mg/m2 is based upon separate data from a phase I pediatric oncology study concluded that the maximum tolerated dose of everolimus in children is 5 mg/m^2/day.[25] In order to optimize patient safety, and to ensure that excessive exposure does not occur, trough concentrations will be assessed initially and monitored as appropriate throughout the study.

Pharmacokinetics of RAD001 in patients with TSC:

During Study RAD001M2301, in patients with TSC who have SEGA, pre-dose (C_{min}) and 2-hour post-dose (C_{2h}) PK blood samples were collected at steady-state. Ages of patients in the Everolimus arm of study ranged from 1 to 23.9 years. Patients in this study received a starting dose of 4.5 mg/m^2/day which was subsequently titrated to a whole blood trough concentration of 5-15 ng/mL. This is the starting dose and trough range approved for this indication.

1.5 Correlative Studies

Biomarkers of mTOR pathway activation and sensitivity to mTOR inhibitors, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated 4EBP1, phosphorylated PRAS40 (pT246), phosphorylated $P70^{S6K}$, and PTEN expression, will be performed. Although these biomarkers have, to varying degrees, been correlated with mTOR pathway activation and sensitivity to mTOR inhibitors, these studies are considered to be exploratory in the context of this clinical trial.

1.6 Examination of H3.K27me3 Expression in Ependymoma

Since 2011, several studies have been published that have segregated pediatric posterior fossa ependymomas by DNA methylation-based methods into subtypes labeled Group A and Group B.[31] Group A ependymomas occur more frequently among children and males and have a poor survival; whereas Group B ependymomas occur more frequently among adults, have equal percentages of males and females, and have a relatively good survival.[31] Panawalker *et al.* recently identified expression of H3.K27me3 by immunohistochemistry as correlating very closely with DNA methylation-based subtyping with very high sensitivity (99%) and specificity (100%) in the ability to distinguish Group A posterior fossa ependymoma from Group B posterior fossa ependymoma.[32] Furthermore, this study and others have determined that low levels of expression of H3.K27me3 by immunohistochemistry are associated with poor event free and overall survival for children with ependymoma.[32-34]

For tumors from subjects enrolled on this protocol, we will perform immunohistochemistry for H3.K27me3 on existing and available FFPE slides on enrolled subjects (and controls) according to established methods to determine ependymoma subtype (either Group A or Group B). Given the population of patients with recurrent ependymoma enrolled on this study, we predict that the majority of enrolled tumors will be classified as Group A. A description of the results will be reported in the manuscript.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

Determine the objective response rate (ORR = Complete Response Rate + Partial Response Rate + Prolonged Stable Disease Rate) following treatment with everolimus for children with recurrent or progressive ependymomas.

2.2 Secondary Objectives

2.2.1 Determine the duration of response, progression free survival (PFS) and event free survival (EFS) following treatment with everolimus for children with recurrent or progressive ependymomas.

2.2.2 Determine safety and tolerability of everolimus among children with recurrent or progressive ependymomas.

2.2.3 Descriptive analysis and correlation of response rate to biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated PRAS40 (pT246), phosphorylated 4EBP1, phosphorylated $P70^{S6K}$, and PTEN expression.

2.3 Endpoints

2.3.1 Objective Response Rate = Complete Response Rate + Partial Response Rate + Prolonged Stable Disease Rate.

2.3.2 Duration of Response

2.3.3 Progression Free Survival

2.3.4 Overall Survival

2.4.5 Dose limiting toxicities

2.4.6 Biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated 4EBP1, phosphorylated PRAS40 (pT246), phosphorylated $P70^{S6K}$, and PTEN expression.

3.0 PATIENT ELIGIBILITY

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient (See Section 9.4) for registration procedures. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The signed informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified. All screening procedures must be performed within 14 days prior to initiation of study therapy (Course 1 Day 1) unless otherwise stated.

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Diagnosis and Age: Ependymoma (WHO grade II) or Anaplastic Ependymoma (WHO grade III) that has relapsed or become refractory to standard therapy. Patients must have had histologic verification of their malignancy at original diagnosis or time of recurrence. Age must be ≥ 2 years and ≤ 21 years of age at study entry.

3.1.2 Performance status: Lansky ≥ 50% for patients ≤ 10 years of age or Karnofsky ≥ 50% for patients > 10 years of age.

3.1.3 Adequate bone marrow function as shown by: ANC ≥ 1000/mm^3, platelets ≥ 100,000/mm^3 and hemoglobin > 9.0 g/dL. Note: these lab parameters must be transfusion-independent

3.1.4 Adequate liver function as shown by:
3.1.4.1 Total serum bilirubin ≤ 2.0 mg/dL.
3.1.4.2 ALT and AST ≤ 2.5x ULN
3.1.4.3 INR ≤ 2.

3.1.5 Adequate renal function: serum creatinine ≤ 1.5x ULN.

3.1.6 Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

3.1.7 Signed informed consent obtained prior to any screening procedures.

3.1.8 Patients must have measurable residual disease, defined as tumor that is measurable in two diameters on MRI. Diffuse leptomeningeal disease is not considered measurable.

3.1.9 Prior Therapy: Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, and radiotherapy prior to participating in this trial.

3.1.9.1 No prior myelosupressive chemotherapy for at least 21 days prior to study enrollment.

3.1.9.2 Must not have received craniospinal radiation therapy within 24 weeks prior to study entry and no involved field radiation therapy for 12 weeks prior to study enrollment.

3.1.9.3 If patients received prior monoclonal antibody treatment, at least three half-lives must be elapsed by the time of treatment initiation.

3.1.9.4 No investigational drugs for 4 weeks prior to study enrollment.

3.1.9.5 No prior therapy with mTOR inhibitors (including sirolimus, temsirolimus or everolimus).

3.1.10 MRI of the brain and the complete spine: All patients must have had an MRI of the brain and spine that has measurable tumor (not only diffuse leptomeningeal tumor) within 14 days prior to study enrollment. Note: Submission of MRIs for central review is required, but is not required to begin therapy. Completion of central review is not required prior to starting treatment (See Protocol Section 6.1.9 for details).

3.1.11 If available, tumor tissue from either initial diagnosis or subsequent surgery will be submitted on Formalin Fixed Paraffin Embedded (FFPE) slides (n = 12) to the Pathology Laboratory at Children's Medical Center-Dallas for correlative biological studies (including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated 4EBP1, phosphorylated PRAS40 (pT246), phosphorylated $P70^{S6K}$, and PTEN expression.) See Section 8.0 for details about submission of these slides. Note: Completion of central review is not required prior to starting therapy.

3.2 Exclusion Criteria

3.2.1 Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).

3.2.2 Concomitant use of medications known to have strong inhibition or induction of CYP3A enzymes is discouraged and should be discussed with the study PI (see Table 4-7 and 4-8 for a list of prohibited medications). Note that systemic corticosteroids (e.g., dexamethasone is a CYP3A inducer) are not allowed. Inhaled corticosteroids are allowed.

3.2.3 Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Everolimus.

3.2.4 Uncontrolled diabetes mellitus as defined by HbA1c > 8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary per standard of care.

3.2.5 Patients who have any severe and/or uncontrolled medical conditions such as:
- 3.2.5.1 Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤6 months prior to start of Everolimus
- 3.2.5.2 Serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease.
- 3.2.5.3 Symptomatic congestive heart failure of New York Heart Association Class III or IV
- 3.2.5.4 Active (acute or chronic) or uncontrolled severe infection,
- 3.2.5.5 Liver disease such as cirrhosis, decompensated liver disease, and chronic hepatitis
- 3.2.5.6 Known severely impaired lung function (spirometry and DLCO 50% or less of normal and O_2 saturation 88% or less at rest on room air)
- 3.2.5.7 Active bleeding diathesis

3.2.6 Known history of HIV sero-positivity.

3.2.7 Patients who have received live attenuated vaccines within 1 week of start of everolimus and during the study. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

3.2.8 Patients who have a history of another primary malignancy, with the exceptions of: non-melanoma skin cancer, and carcinoma in situ of the cervix, uteri, or breast from which the patient has been disease free for ≥3 years.

3.2.9 Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study.

3.2.10 Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing.

3.2.11 Pregnant or nursing (lactating) women.

3.2.12 Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment. Women of childbearing potential should be advised to use a highly effective method of contraception while receiving everolimus, and for up to 8 weeks after ending treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomized male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)

c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

- In case of use of oral contraception women should have been stable on the oral agent before taking study treatment.

3.2.13 Contraception Use

- During the course of the clinical trial, sexually active males must use a condom during intercourse while taking the drug and should not father a child in this period and for up to 8 weeks after stopping treatment.
- A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
- Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.
  Female patients of childbearing potential must have a negative beta-human chorionic gonadotropin (β-hCG) pregnancy test at time of screening (urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing)

3.2.14 Screening for hepatitis B:
Prior to start of Everolimus, the following three categories of patients should be tested for hepatitis B viral load and serologic markers, that is, HBV-DNA, HBsAg, HBs Ab, and HBc Ab.

3.2.14.1 All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal and Greece. [http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.htm]

3.2.14.2 Patients with any of the following risk factors:

- known or suspected past hepatitis B infection,
- blood transfusion(s) prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact with hepatitis B infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos,
- mother known to have hepatitis B
- history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
- Additional patients at the discretion of the investigator

3.2.14.3 Screening for hepatitis C: Patients with any of the following risk factors for hepatitis C should be tested using quantitative RNA-PCR:

- known or suspected past hepatitis C infection (including patients with past interferon ‘curative’ treatment),
- blood transfusions prior to 1990,
- current or prior IV drug users,
- current or prior dialysis,
- household contact of hepatitis C infected patient(s),
- current or prior high-risk sexual activity,
- body piercing or tattoos.

3.2.14.4 At the discretion of the investigator, additional patients may also be tested for hepatitis C.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

The investigational treatment is Everolimus; it will be administered in conjunction with best supportive care. Best supportive care includes all care provided to patients deemed necessary by the treating physician, such as analgesics and anti-diarrheal therapies.

- Everolimus will be administered by mouth at a starting dose of 4.5 mg/m^2/day. Each course of therapy will last for 28 days for up to 24 courses.
- The starting dose 4.5 mg/m^2 of Everolimus will be titrated upward (or downward), subject to tolerability, with the objective of achieving trough Everolimus levels in the range of 5-15 ng/mL.
- All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.
- Medication labels will comply with US legal requirements and be printed in English. Additional labels may be used in the primary language of the study participant. They will supply no information about the patient. The storage conditions for Everolimus will be described on the medication label.

4.2 Treatment Assignment

This is a single arm, open label, phase II study of Everolimus for children with recurrent or progressive ependymomas.

Dosing Regimen

The investigator should promote adherence by instructing the patient to take the study drug exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the study drug as prescribed.

4.3 Medication Formulations, Dosage and Administration

4.3.1 Everolimus is supplied by Novartis. Everolimus should be administered orally, once daily at the same time every day either consistently with food or consistently without food. Everolimus is available as dispersible tablets.

4.3.2 The dose of Everolimus is 4.5 mg/m^2/day administered once a day. The initial calculated dose of Everolimus will be rounded either up or down to the nearest possible dose based upon available Dispersible Tablets (see section 4.4.3 below).

4.3.3 Everolimus will be supplied in the form of Dispersible Tablets (also referred to as 'tablets for oral suspension'): 2 mg, 3 mg and 5 mg.

4.3.4 Everolimus may be administered by either of the following two methods:

4.3.5 **Method 1, Using an oral syringe:** The required number of dispersible tablets (maximum of five 2 mg tablets, three 3 mg tablets, or two 5 mg tablets) should be placed into a 10 mL oral syringe. The plunger should be inserted and pushed inward to make contact with the dispersible tablet(s). A sufficient volume of water (approximately 5 mL) should be drawn up from a glass to cover the dispersible tablet(s). In addition, approximately 4 mL of air should be drawn up into the oral syringe. The filled oral syringe should be placed in a glass (tip up) and the contents left to disintegrate for 3 minutes. Prior to administration, the oral syringe should be inverted gently five times. While holding the oral syringe in an upright (tip up) position, excess air should be removed carefully. The full contents of the oral syringe should be immediately dispensed into the mouth of the patient, slowly and gently. The same volume of water and air should then be drawn up into the oral syringe, and the contents should be swirled to suspend any remaining particles. The contents should be administered as previously described to ensure the entire dose is administered.

4.3.6 **Method 2, Using a small drinking glass:** The required number of dispersible tablets (maximum of five 2 mg tablets, three 3 mg tablets, or two 5 mg tablets) should be placed into a small drinking glass (maximum size 100 mL) containing approximately 25 mL of water. The tablets should be left to disintegrate for 3 minutes. The contents should be stirred gently with a spoon, immediately prior to drinking. The glass should be rinsed with the same volume of water and stirred with the same spoon to suspend any remaining tablet particles. The rinse should be swallowed to ensure the entire dose is administered.

4.3.7 If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

4.4 Medication Supply and Accountability

4.4.1 Supplier: Everolimus tablets are supplied by Novartis and distributed through Biologics. Do not use commercial supply.

4.4.2 Agent Ordering: Sites will be provided the information for ordering drug supplies in the Study Procedures Manual.

4.4.3 Agent Accountability: The investigator is responsible for study medication accountability, reconciliation, and record maintenance. In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of investigational product dispensed and/or administered to study subjects, the amount returned by study subjects (if applicable), and the amount received from and returned to Biologics, when applicable. Product accountability records must be maintained throughout the course of the study.

After completion of the study, a final inventory of accountability records and unused study medications will be performed by the study monitor and site personnel. A record of the number of tablets dispensed to and returned by each subject at each visit must be maintained and reconciled with the study medication and compliance records in the eCRF. The cause of any missed doses should be discussed and documented.

Any AE(s) associated with missed doses must be recorded in the eCRF. Subjects should be instructed for the importance of compliance to study treatments.

An example study drug diary log is included in the protocol in Appendix III.

4.5 Recommended Dose of Everolimus

The recommended starting dose is 4.5 mg/m^2/dose, once daily. Continue treatment for up to 2 years, until disease progression or unacceptable toxicity occurs. After 2 years of therapy, patients will complete the study protocol, but may continue therapy using commercially available drug based upon the clinical judgment of their treating physician and the child's parents or guardians.

4.5.1 **Dose modification and dose delay**

4.5.1.1 Therapeutic drug monitoring: Therapeutic drug monitoring of Everolimus blood concentrations is required for patients enrolled on study and taking Everolimus. Testing is to be performed by Quest Diagnostics using a validated bioanalytical LC/MS method (test code 18883X). Trough concentrations should be assessed 2 weeks (+/- 4 days) after the initial dose, after any change in dose or formulation, after an initiation or change in co-administration of CYP3A4 inducers or inhibitors, or after any change in hepatic status.

4.5.1.2 Dosing modifications:

Titrate the dose to attain trough concentrations of 5 to 15 ng/mL.

- For trough concentrations less than 5 ng/mL, increase the daily dose by 2 mg and repeat trough concentration in 2 weeks (+/- 4 days).
- For trough concentrations greater than 15 ng/mL, reduce the daily dose by 2 mg and repeat trough concentration in 2 weeks (+/- 4 days).
- The lowest possible dose level of Everolimus is 2 mg daily.
- If dose reduction is required for patients receiving the lowest available strength, administer every other day.

- For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Dose levels are as follows: Level -2 = 3 mg/m^2/dose, Level -1 = 3.8 mg/m^2/dose, Level 0 = 4.5 mg/m^2/dose, Level +1 = 5.2 mg/m^2/dose and Level +2 = 6 mg/m^2/dose. If dose adjustments need to be made for toxicity, patients' doses of Everolimus should not be targeted to achieve a trough level of 5 – 15 ng/mL.

Table 4-1 Dosing guidelines for Everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Please refer to Table 4-3.
Reactivation of HBV or HCV flare	Please refer to Table 4-5.
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt Everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)*	Interrupt Everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be re-started at one dose level lower. If resolution takes > 7 days, discontinue Everolimus.
Recurrence of Grade 4 AST or ALT elevation after dose reduction or toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus.
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia	Interrupt Everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other grade 4	Hold Everolimus until recovery to grade ≤ 1 or baseline value Reintroduce Everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue Everolimus
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of Everolimus is 2 mg daily. Below this level, Everolimus must be discontinued.
Recurrence of grade 4 after dose reduction	Discontinue Everolimus
Any non-hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus

* Should HCV flare be confirmed, the guidelines for flare must take precedence (Table 4-4).

Table 4-2 Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, ≥ 50x109/L)	Interrupt Everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce Everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt Everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce Everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x109/L)	Interrupt Everolimus until recovery to grade ≤ 1. Then reintroduce Everolimus at one dose level lower, if available.
Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x109/L)	Interrupt Everolimus until resolution to grade ≤2 or baseline value If AE resolution occurs ≤ 7 days, reintroduce Everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Interrupt Everolimus until recovery to grade ≤ 2 or baseline value. Reintroduce Everolimus at one dose level lower, if available.*
Grade 3 febrile neutropenia	Interrupt Everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce Everolimus at one dose level lower, if available.*
Grade 4 febrile neutropenia	Discontinue treatment
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of Everolimus is 2 mg daily.Below this level, Everolimus must be discontinued.
*Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction	Discontinue Everolimus
*Any hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus

4.5.2 Management of specific toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.
Adverse events most frequently observed with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2). Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in Table 4-1, 4-2, 4-3, 4-4, 4-5 and 4-6.

4.5.3 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking Everolimus Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with Everolimus. Treat pre-existing infections prior to starting treatment with Everolimus. While taking Everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Everolimus.
If a diagnosis of invasive systemic fungal infection is made, discontinue Everolimus and treat with appropriate antifungal therapy.

4.5.4 Management of skin toxicity

For patients with grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

4.5.5 Management of stomatitis / oral mucositis / mouth ulcers

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa e.g. gastroesophageal reflux disease (GERD) and pre-existing stomatitis/mucositis must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to

their strong inhibition of Everolimus metabolism, therefore leading to higher Everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

4.5.6 Management of diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset at age and weight appropriate doses.

4.5.7 Management of hyperlipidemia and hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with lifestyle and dietary changes, in addition to an appropriate triglyceride-lowering medication approved for children, such as fish oil or fenofibrate.[31]

Hyperglycemia has been reported in clinical trials. Monitoring of fasting serum glucose is recommended prior to the start of Everolimus and periodically thereafter. Optimal glycemic control should be achieved before starting a patient on Everolimus.

4.5.8 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.
- Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Everolimus therapy without dose alteration.

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. In addition, pulmonary function tests (PFTs) can be conducted, if clinically indicated, to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in Table 4-3 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 4-3 Management of non-infectious pneumonitis

Worst grade pneumonitis	Required investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus until symptoms improve to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt Everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue Everolimus.

4.5.9 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy.[32] Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality.[33] A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

4.5.10 Monitoring and prophylactic treatment for hepatitis B reactivation.

Table 4-4 provides details for monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 4-4 Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of Everolimus Monitor HBV-DNA approximately every 4-8 weeks		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of Everolimus. For HBV reactivation definition and management guidelines, see Table 4-5.

Table 4-5 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBsAg ---------- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	Treat: Start a second antiviral medication AND Interrupt Everolimus administration until resolution: • ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days, Everolimus should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of Everolimus. If resolution occurs > 28 days Patients should discontinue Everolimus but continue both antiviral therapies at least 4 weeks after last dose of Everolimus.
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb] ---------- Reactivation is defined as: New appearance of measurable HBV-DNA	Treat : Start first antiviral medication AND Interrupt Everolimus administration until resolution: • ≤ undetectable (negative) HBV-DNA levels If resolution occurs within ≤ 28 days, Everolimus should be re-started at one dose lower, if available . If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of Everolimus. If resolution occurs > 28 days Patients should discontinue Everolimus but continue antiviral therapy at least 4 weeks after last dose of Everolimus.

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 4.03 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

4.5.11 Monitoring for hepatitis C flare

The following two categories of patients should be monitored every 4–8 weeks for HCV flare:

- Patients with detectable HCV RNA-PCR test at screening.
- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered 'cured')

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to
Table 4-6.

Table 4-6 Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 4.03 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

4.6 Concomitant Medications

Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

4.6.1 **Permitted concomitant therapy:** Other than study medications, patients may take other supportive therapies as prescribed by their treating physician. Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted.

4.6.2 **Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates:** Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus . Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used

prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.

- Grapefruit or citrus juices affect P450 and PgP activity. Concomitant use should be avoided.
- Concommitant use of medications known to have inhibition or induction of CYP3A enzymes is strongly discouraged and should be discussed with the study chair. If patients begin therapy with strong CYP3A inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), perform Everolimus trough concentration in 2 weeks. Enzyme induction usually occurs within 2 weeks.
- For patients with low Everolimus trough concentrations (< 5 ng/ml), increase doses by 33% and repeat trough concentration in 2 weeks.
- For patients with elevated Everolimus trough levels (>15 ng/ml), decrease dose by 25% and repeat trough concentration in 2 weeks.
- Co-administration with strong inducers or inhibitors of CYP3A4 is strongly discouraged and should be discussed with the study chair. If a patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort), an increase in the dose of Everolimus may be necessary. Enzyme induction usually occurs within 2 weeks; therefore Everolimus dose should be increased by one increment 7 days after the start of the inducer therapy. If no safety concerns are seen within the next 7 days, the dose can be increased again one additional increment up to a maximum of twice the daily dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of Everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 4-7 listing relevant inducers and inhibitors of CYP3A and Table 4-8 for a list of relevant substrates, inducers, and inhibitors of PgP.

Table 4-7 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers:
carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate, avasimibe, bosentan, etravirine, nafcillin, ritonavir, talviraline (not available in US market), tipranavir, amprenavir, aprepitant, armodafinil (R-modafinil), dexamethasone, nevirapine, prednisone, pleconaril (not available in US market), rufinamide
Inhibitors:
Strong inhibitors: clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, tipranavir, elvitegravir, Posaconazole (Krishna et al 2009) Moderate inhibitors: aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice (citrus parasidi fruit juice), imatinib, tofisopam, verapamil, amprenavir, fosamprenavir, dronedarone

Table 4-8 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates:
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel
Inducers:
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors:
amiodarone, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, ginkgo (ginkgo biloba), indinavir, itraconazole, , lopinavir, mibefradil, milk thistle (silybum marianum), nifedipine, nitrendipine, quercetin, quinidine, ranolazine, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, telmisartan, tipranavir, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

4.6.3 **Vaccinations:** Immunosuppressants may affect the response to vaccination and vaccination during treatment with Everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with Everolimus Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

4.6.4 **Wound healing complications:** Impaired wound healing is a class effect of rapamycin derivatives, including everolimus. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period.

4.6.5 **Prohibited concomitant therapy** Anti-neoplastic therapies: Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted until disease progression is documented per RECIST. Palliative radiotherapy or surgery is not allowed.

4.7 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

4.8 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 2 years or until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.9 Duration of Follow Up

Patients will be followed after removal from treatment or until death, whichever occurs first. Follow-up for survival will occur by the treating oncologist and will be communicated to the PI or designee at 6-month intervals by phone or medical record review. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.10 Removal of Patients from Protocol Therapy

Patients will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the patient was removed in the Case Report Form. The patient should be followed-up per protocol.

4.11 Patient Replacement

If a patient is withdrawn from the study prior to completing 1 course of therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before signed informed consent was obtained.

5.1.1 All screening procedures must be performed within 14 days prior to Course 1 Day 1 unless otherwise stated.

5.1.2 Screening medical history, including complete medical and surgical history, history of infections, and MRI of the brain and spine

5.1.3 Demographics, including age, gender, race, ethnicity

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs (temperature, pulse, respirations, blood pressure, pulse oxygenation), height, weight, neurologic exam

5.1.7 Performance status, (Lansky Play Scale for children ≤ 10 years of age, Karnofsky Performance Level for patients > 10 years of age.)

5.1.8 Adverse event assessment: Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.9 Hematology: CBC with differential

5.1.10 PT/PTT/INR

5.1.11 Serum chemistries to include: alkaline phosphatase, ALT, AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides)

5.1.12 Hepatitis serology, including HBsAg, HBsAb, HBcAb, Hep C RNA for patients at risk of hepatitis as defined in Section 3.2.14.

5.1.13 Pregnancy test (for females of child bearing potential), See section 3.2.13 for definition.

5.1.14 Informed Consent

5.1.15 Tumor assessment:
5.1.15.1 Central Pathology Review
5.1.15.2 Correlative biology studies (12 unstained FFPE slides)

5.2 Procedures During Treatment

5.2.1 **Monthly (+/- 7 days):**

- Physical exam (including neurologic exam), vital signs, performance status
- Pulse Oximetry
- CBC with differential
- Serum Chemistries to include: alkaline phosphatase, ALT, AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides)
- PT/PTT/INR
- Urine pregnancy test for females of childbearing potential (Section 3.2.12)
- AE Assessment
- Review of Concomitant Medications
- Drug Accountability Review
- Everolimus trough levels will be tested 2 weeks after starting protocol therapy. Repeat testing may be required if there are dose adjustments or other parameters met as defined in Section 5.2.4.

5.2.2 **Assessment of Tumor Response:**

- MRI of the brain and spine: MRI of the brain and spine should be performed every other month for the first year, every third month for the second year, and whenever clinically indicated. Specifically, prior to courses 3, 5, 7, 9, 11, 13, 16, 19, 22, and then at the end of treatment (after course 24). Note: MRI should be completed within 7 days *before* the start of the indicated cycles.
- Lumbar puncture for cytology: Not required, but to be performed as clinically indicated

5.2.3 **Within 30 days after treatment termination:**

- Physical exam (including neurologic exam), vital signs, performance status
- CBC with differential
- Serum Chemistries to include: alkaline phosphatase, ALT, AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, fasting glucose,

potassium, sodium, chloride, bicarbonate, uric acid, LDH, fasting lipid panel (LDL, total cholesterol, triglycerides).
- PT/PTT/INR
- Urine pregnancy test for females of childbearing potential (Section 3.2.12)
- Hepatitis serology, including HBsAg, HBsAb, HBcAb, Hep C RNA for patients at risk of hepatitis as defined in Section 3.2.14.
- AE Assessment
- Review of Concomitant Medications
- Drug Accountability Review

5.2.4 **Pharmacokinetic Drug Monitoring and Adjustments:**

The target drug trough level of Everolimus is 5 – 15 ng/ml.
- Everolimus trough levels will be assessed 2 weeks (+/- 4 days) after starting drug. If the level is outside of the target range, then the dose should be adjusted to achieve a trough level of 5 – 15 ng/ml. Trough levels should be assessed within one hour before taking the daily dose.
- Whenever any dose adjustment of Everolimus occurs, trough levels should be reassessed two weeks (+/- 4 days) following the adjustment to ensure that the new dose achieves the target drug trough level of 5-15 ng/ml.
- Furthermore, Everolimus trough levels should be assessed 2 weeks (+/- 4 days) following the starting, ending, or changing of the dose of inducers or inhibitors of CYP3A4 or P-glycoprotein.

5.3 Follow-up Procedures

Patients will be followed for survival after completion of (or early withdrawal from) study treatment or death.

Adverse Events and concomitant medication monitoring should be continued for at least 30 days following the last dose of study treatment.

5.4 Time and Events Table

(See Appendix II)

5.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Patient voluntarily withdraws from treatment (follow-up permitted);

5.5.2 Patient withdraws consent (termination of treatment and follow-up);

5.5.3 Patient is unable to comply with protocol requirements;

5.5.4 Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);

5.5.5 Patient experiences toxicity that makes continuation in the protocol unsafe;

5.5.6 Treating physician judges continuation on the study would not be in the patient's best interest;

5.5.7 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.5.9 Lost to follow-up: If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 MEASUREMENT OF EFFECT

6.1 Response Assessment

6.1.1 Definitions

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

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 definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

In this study, response and progression will be evaluated using the International Society of Pediatric Oncology Brain, Tumor Subcommittee for the Reporting of Trials criteria shown below with slight modification.[34] Response will be assessed by magnetic resonance imaging (MRI) scan every 8 weeks (every 2 cycles) for 1 year, then every 12 weeks.

6.1.2 Complete Response (CR):

Complete disappearance on MRI of all enhancing tumor and mass effect, on a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses), accompanied by a stable or improving neurologic examination and must be sustained for at least 4 weeks. If cerebral spinal fluid (CSF) evaluation was positive, it must become negative. CSF negativity has to be confirmed at least two times at consecutive samplings if the CSF was positive.

6.1.3 Partial Response (PR):

Greater than or equal to 50% reduction in tumor size by bi-dimensional measurement on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination and must be sustained for at least 4 weeks.

6.1.4 Minor Response (MR):

Greater than or equal to 25% to < 50% reduction in tumor size by bi-dimensional measurement on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination and must be sustained for at least 4 weeks.

6.1.5 **Stable Disease (SD):**
Neurologic examination is at least stable and maintenance corticosteroid dose is not increased, and MRI meets neither the criteria for MR nor the criteria for progressive disease and must be sustained for at least 8 weeks.

6.1.6 **Stable Disease (SD):**
Neurologic examination is at least stable and maintenance corticosteroid dose is not increased, and MRI meets neither the criteria for MR nor the criteria for progressive disease and must be sustained for at least 8 weeks.

6.1.6.1 **Prolonged Stable Disease** is defined as stable disease for at least 6 months duration.

6.1.7 **Progressive Disease (PD):**
Progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (eg, anticonvulsant or corticosteroid toxicity, electrolyte disturbances, sepsis, hyperglycemia, etc), OR a greater than 25% increase in the bi-dimensional measurement on MRI, OR the appearance of a new lesion or new CSF positivity, OR increasing doses of corticosteroids required to maintain stable neurologic status or imaging.

All patients who have measurable disease according to the above response criteria, who received at least 1 cycle of therapy and who have their disease re-evaluated will be evaluable for response. All sites of disease should be followed as either target or nontarget lesions, as categorized at baseline. All measurable lesions up to a maximum of 5 lesions should be identified as target lesions, while all other lesions (either additional measurable lesions or nonmeasurable lesions) should be classified as nontarget lesions. If possible, the same method, radiological or physical, should be employed and assessed by the same individual on each occasion. If possible, the same method should be employed and assessed by the same institution on each occasion. Ideally, any response should be confirmed by repeated evaluation at least 28 days after the first assessment where the response criteria were met.

6.1.8 **Response Review**
Patients who have a confirmed response (CR, PR, MR, or prolonged SD) as deemed by the institution will have the response reviewed by an independent expert. Radiological images will be collected only for those patients who require central response review.

6.1.9 **Central Review of Imaging:**
All required MRIs of the brain and spine with gadolinium contrast will be loaded onto a CD in DICOM format and sent to the address below for central review. Please send an e-mail notification (including tracking number) to the study PI at time of shipping. Note that central review is not required prior to starting therapy, but MRI's should be submitted for central review concurrently with patient enrollment. In the unlikely event that central review does not agree with the local read, the patient will immediately be removed from the protocol and discontinue study drug if study drug had been started. Patients removed from protocol in this fashion will be replaced.

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6.1.10 **Evaluation of Best Overall Response**

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

Table 6-1

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.11 **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 recurrent disease is objectively documented.

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

6.1.12 **Progression-Free Survival**

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.1.13 **Event-Free Survival**

Event-Free Survival (EFS) is defined as the duration of time from start of treatment to: (1) disease progression; (2) second malignant neoplasm; (3) death regardless of cause; or (4) date of last contact, whichever comes first.

6.2 Safety/tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.03 (download: **http://ctep.cancer.gov/reporting/ctc.html**) for adverse event reporting.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

7.1.1

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of the subject's safety and care. Adverse events not requiring expedited reporting will be entered into the eCRF on a monthly basis.

All subjects experiencing an adverse event, regardless of its relationship to study drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2.1 **Definitions**

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious Adverse Event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

*Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery that prolongs the existing hospitalization, those events should be evaluated and/or reported as SAEs.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded, and followed as appropriate.

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the patient's eCRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and

symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates or if continuing at the Safety Follow-up Visit)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, hospitalized, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Sections 7.2.1 and 7.4.1.

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment

Laboratory Test Abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

7.2.2 **Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):**

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the regulations for the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56. 108(b)(1) and 21 CRF 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;***AND***
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; ***AND***
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 **UTSW Reporting Requirements**

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 5 business days of the center learning of the event.

7.2.3.1 UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. (See Appendix IV of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).

All SAE/UPIRSOs at all sites, which occur in research participants on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs/UPIRSOs occurring during the protocol-specified monitoring period should be submitted to the SCCC DSMC within 5 business days of the PI or delegated study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA

Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE/UPIRSO documentation hat is available area also submitted to the DSMC Chair who determines if further action is required.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW, Simmons Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs/UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Investigator: Daniel C. Bowers, MD 214-648-8594 (business hours) or 214-456-7000 (nights and weekends) UTSW SCCC Data Safety Monitoring Committee Coordinator (if fax report is not available) within 5 working days to 214-648-7097.
Written reports to: Investigator: Daniel C. Bowers, MD, Department of Pediatrics - Oncology 5323 Harry Hines Blvd. Dallas, TX 75390 Fax: 214-456-6151 214-648-8594 (business hours) or 214-456-7000 (nights and weekends) RAD001C224T@childrens.com UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7018 or deliver to NB 2.418 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Serious adverse events occurring at sites other than UT Southwestern Medical Center will be promptly (less than 2 business days) reported to phone: 469-354-8137 and Dr. Daniel Bowers. These adverse events will be evaluated as whether or not they are related to study participation.

Serious adverse events (SAEs) for studies where SCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 5 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 5 days of PI awareness of the event (life threatening or fatal events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction).

Local UPIRSOs (non-serious events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness.

External UPIRSOs including those that occur as non-local events, require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure
- the study agent's background and associated known toxicities section of this protocol.

7.4 Serious Adverse Events

7.4.1 Definitions

A serious adverse event is an undesirable sign, symptom or medical condition which:
- is fatal or life-threatening

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

7.4.2 Reporting Requirements

The principal investigator, Dr. Bowers, has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

To ensure patient safety, every SAE, regardless of suspected causality, occurring:

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

must be reported to Novartis within 24 hours of learning of its occurrence **(fax: 877-778-9739)**This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of

the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Everolimus Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the comparator drug company by the investigator.

7.5 Pregnancy

Preclinical data regarding reproductive toxicity is described in the most recent Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.6 Stopping Rules

Occurrence of >30% of patients requiring permanent discontinuation of Everolimus in this study (i.e., 4 of the first 10 patients or 6 of the first 16 patients) will lead to stopping this study. A minimum of six patients will be treated.

8.0 CORRELATIVE STUDIES

8.1 FFPE

Optional submission of tumor tissue, submitted as Formalin Fixed Paraffin Embedded (FFPE) tissue on 12 glass slides will be submitted to the study coordinating site within 28 days of Course 1 Day 1. Slides will be identified by study participant number.

8.2 Immunohistochemistry

Immunohistochemistry will be performed for biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated

PRAS40 (pT246), phosphorylated 4EBP1, phosphorylated $P70^{S6K}$, and PTEN expression.

8.2.1 Intensity of immunohistochemistry staining for each biomarker will be scored as Negative (-); weakly positive (+); moderately positive (++); and strongly positive (+++).

8.2.2 Results of intensity of immunohistochemistry staining will be described and correlated with tumor response to Everolimus.

Send slides to the address below and clearly label package as CRAD001 study. Also, send an e-mail notification at time of shipping to the Study PI <Daniel.Bowers@UTSouthwestern.edu>, study coordinator <RAD001C224T@childrens.com>, and Dr. Rajaram <Veena.Rajaram@childrens.com> including tracking number. Central review is not required prior to starting therapy.

Veena Rajaram, MD
Department of Pathology
Children's Medical Center – Dallas
1935 Medical District Drive
Dallas, TX 75235

8.2.3 Immunohistochemistry will be performed on FFPE tumor tissue on slides for H3.K27me3 according to established methods. Based upon staining, tumors will be classified as Ependymoma Group A (negative – light staining) or Ependymoma Group B (positive staining). Descriptive results will be reported in the manuscript.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

The study is a prospective single-arm multi-center phase II study that determines the objective response rate following treatment with everolimus for children with recurrent or progressive ependymomas. Given the relatively small study sample size, descriptive statistics will be used to report the results of the study.

Study endpoints include the following:

- Objective Response Rate = Complete Response Rate + Partial Response Rate + Prolonged Stable Disease Rate.
- Duration of Response
- Progression Free Survival
- Overall Survival
- Dose-limiting toxicities
- Biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated PRAS40 (pT246), phosphorylated 4EBP1, phosphorylated $P70^{S6K}$, and PTEN expression.

9.2 Sample Size and Accrual

Simon's two-stage optimal design[35] is used to compute the number of patients to be recruited for this phase II trial. The null hypothesis that the true objective response rate (ORR) is 10% will be tested against a one-sided alternative. In the first stage, 7 patients will be accrued. If there is no ORR seen in these 7 patients, the study will be stopped.

Otherwise, 11 additional patients will be accrued for a total of 18 patients. The null hypothesis will be rejected if 4 or more ORRs are observed in 18 patients. This design yields a type I error rate of 10% and power of 80% when the true ORR is 30%. It is expected that the accrual will be completed in 2 years since 9 patients are expected to be recruited in a year.

9.3 Data Analyses Plans

Objective response rate and the corresponding 95% confidence interval will be estimated using the exact binomial method. Kaplan-Meier method will be used to estimate the duration of response, progression free survival (PFS) and event free survival (EFS) following treatment with everolimus for children with recurrent or progressive ependymomas. The corresponding 95% confidence interval will be computed using Greenwood's formula. Safety and tolerability of everolimus will be estimated using exact binomial method. Exploratory analysis will be conducted to investigate the correlation between response rate and biological markers of mTOR pathway activation, including phosphorylated $S6^{235/236}$, phosphorylated $S6^{240/244}$, phosphorylated PRAS40 (pT246), phosphorylated 4EBP1, phosphorylated $P70^{S6K}$, and PTEN expression.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Conflict of Interest Office at their respective institution. All investigators will follow the University conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient or their legally authorized representative and by the person who conducted the informed consent discussion.

10.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office, Pauline Allen Gill Center for Cancer and Blood Disorders, Children's Medical Center – Dallas.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal Wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if this institution holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract
- Site Delegation Log

10.4 Registration Procedures

All patients must be registered with the UT Southwestern Medical Center / Children's Medical Center-Dallas (UTSW/CMC) Research Office before consenting to study participation. Prior to enrollment, eligibility criteria must be confirmed with the Clinical Research Office Study Coordinator at UTSW/CMC. To register a patient, call 214-456-6167 Monday through Friday, 8:00AM-4:00PM CST. After hours, Daniel C. Bowers, MD (Study Principle Investigator) can be reached through the Children's Medical Center paging operator at 214-456-7000.

10.5 Data Management and Monitoring / Auditing

REDCap is the UTSW SCC institutional choice for electronic data capture of case report forms for this and all SCC investigator initiated trials. REDCap will be used for electronic data capture case report forms in accordance with Simmons Cancer Center requirements.

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials as instructed by the study team to facilitate remote source to case report form verification.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance timelines and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during the internal audit.

The UTSW Simmons Cancer Center (SCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and unanticipated problems in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for Clinical Research Office provides periodic auditing of clinical research documents to insure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way frequency of DSMC monitoring is dependent

upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study, the type of investigational agent, device or intervention being studied, and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol specific DSMC plans must be consistent with these principles.

10.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, a IRB modification form must be completed within five (5) business days of making the change.

10.6.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator and IRB, please follow the guidelines below:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

10.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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APPENDIX I: Inclusion / Exclusion Checklist

Inclusion Criteria—Complete each box with an "X" to confirm patient meets listed criteria	
	Diagnosis and Age: Ependymoma (WHO grade II) or Anaplastic Ependymoma (WHO grade III) that has relapsed or become refractory to standard therapy. Patients must have had histologic verification of their malignancy at original diagnosis or time of recurrence.
	Age must be ≥ 2 years and ≤ 21 years of age at study entry.
	Performance status: Lansky ≥ 50% for patients ≤ 10 years of age or Karnofsky ≥ 50% for patients > 10 years of age.
	Adequate bone marrow function as shown by: ANC ≥ 1,000/mm^3, platelets ≥ 100,000/mm^3 and hemoglobin > 9.0 g/dL. (These values must be transfusion independent)
	Adequate liver function as shown by: Total serum bilirubin ≤ 2.0 mg/dL, ALT and AST ≤ 2.5x ULN, INR ≤ 2.
	Adequate renal function: serum creatinine ≤ 1.5x ULN.
	Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5x ULN (See protocol for exception).
	Signed informed consent obtained prior to any screening procedures
	Patients must have measurable residual disease, defined as tumor that is measurable in two diameters on MRI. Diffuse leptomeningeal disease is not considered measurable.
	Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, and radiotherapy prior to participating in this trial (see protocol for details).
	All patients must have an MRI of the brain and the complete spine that has measurable tumor (not only diffuse leptomeningeal tumor) within 14 days prior to study enrollment.
	If available, tumor tissue from either initial diagnosis or subsequent surgery will be submitted on Formalin Fixed Paraffin Embedded (FFPE) slides (n = 12) to the Pathology Laboratory at Children's Medical Center-Dallas for correlative biological studies.
Exclusion Criteria—Complete each box with "No" or "NA", as appropriate, to confirm eligibility	
	Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs.
	Concomitant use of medications known to have inhibition or induction of CYP3A enzymes (see Table 4-7 and 4-8 for a list of prohibited medications). Note that systemic corticosteroids (e.g., dexamethasone is a CYP3A inducer) are not allowed. Inhaled corticosteroids are allowed.
	Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Everolimus.
	Uncontrolled diabetes mellitus as defined by HbA1c > 8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
	Patients who have any severe and/or uncontrolled medical conditions (see protocol)
	Patients with a known history of HIV sero-positivity
	Patients who have received live attenuated vaccines (see protocol for examples) within 1 week of start of Everolimus.
	Patients who have a history of another primary malignancy (see protocol for exceptions).
	Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study.
	Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing.
	Pregnant or nursing (lactating) women.
	Women of child-bearing potential unless they are using highly effective methods of contraception (see protocol for details).
	Sexually active males unless they are using a condom (see protocol for details).
	Hepatitis screening must be completed if necessary (see protocols for details).

I have reviewed the eligibility criteria and confirm the patient is eligible for enrollment.

Physician Signature: _____ Date: _____

APPENDIX II: Time and Events Table

Period/Procedure	Screening	Course 1	Courses 2-24 [10]	End of Treatment Visit [13]	Long Term Follow Up
Study Day/Visit Day	**-14 to 1**	**Day 14 (+/- 4 days)**	**Day 1 (+/-7 days)**	**Within 30 Days**	
Informed Consent	X				
Central Review of Pathology and MRI [1]	X				
AE Assessment	X		X	X[14]	
Concomitant Medications	X		X	X[14]	
Drug Accountability			X	X	
Clinical procedures					
Physical Exam	X		X	X	
Vital Signs	X		X	X	
Medical History	X				
Performance Status	X		X	X	
Neurologic Exam	X		X	X	
Pulse Oximetry [2]	X		X		
Laboratory procedures					
CBC w/ Diff [3]	X		X	X	
Blood Chemistry [4]	X		X	X	
Coagulation [5]	X		X	X	
Pregnancy Test (HCG) [6]	X		X	X	
Hepatitis (If Required) [7,8]	X			X	
Everolimus PK Test [9]		X			
Disease Assessment & Outcomes					
Imaging (MRI) [11]	X		X* [11]	X	
Lumbar Puncture (optional) [12]	X		X	X	
Survival Follow Up & Other Treatment					X[15]

[1] Central review of pathology/MRI should be completed concurrently with registration, but is not required before starting therapy.
[2] If pulse oximetry is less than 93% on room air patient should get a CXR monthly until pulse oximetry is >93%.
[3] Including CBC with differential
[4] Including alkaline phosphatase, ALT. AST, total bilirubin, calcium, phosphorus, BUN, creatinine, total protein, albumin, glucose, potassium, sodium, chloride, bicarbonate, uric acid, LDH, and lipid panel (LDL, total cholesterol, triglycerides)
[5] Including PT/PTT/INR
[6] For females of child bearing potential, urine or serum pregnancy test as per your institutional guidelines. See Section 3.1.12 for further details.
[7] Including HBsAg, HBsAb, HBcAb, Hep C RNA. See Protocol Section 3.2.14 for details.
[8] Patients who test positive for hepatitis B antibodies without receiving prior vaccination will be monitored for HBsAg every 4 weeks.
[9] PK testing should also be performed 2 weeks post any Everolimus dose adjustment or any CYP3A4 concomitant medication administration/dose adjustment. See Protocol Section 5.2.4 for details.
[10] Courses are 28 days in length. Each subsequent course following course 1 should begin within 7 days of the end of the prior course.
[11] MRI of the brain and spine will be performed at the beginning of courses 3, 5, 7, 9, 11, 13, 16, 19, 22, and at the end of treatment visit (after course 24). This assessment should be performed on day 1 of these courses as possible, but may be performed up to 7 days prior to starting these courses if necessary.
[12] Lumbar puncture for cytology is optional but may be performed if clinically indicated.
[13] The End of Treatment Visit should be completed within 30 days of treatment termination.
[14] Adverse event and concomitant medication monitoring should be continued for at least 30 days following the last dose of study treatment
[15] Survival follow up will be completed by phone or medical record review.

APPENDIX III: Patient Drug Diary

Patient Drug Diary – CRAD001CUS224T

Instructions: Please fill out the diary every day using the format given in the example below.

DAY	DATE	TIME	DOSE	NUMBER OF CAPSULES?			COMMENTS
				2 mg	3 mg	5 mg	
1	*9/12/09*	*7 : 10* AM PM	8 mg	-	1	1	*He felt nauseated after taking pills.*

DAY	DATE	TIME	DOSE	NUMBER OF CAPSULES?			COMMENTS
				2 mg	3 mg	5 mg	
1		: AM PM					
2		: AM PM					
3		: AM PM					
4		: AM PM					
5		: AM PM					
6		: AM PM					
7		: AM PM					
8		: AM PM					
9		: AM PM					
10		: AM PM					
11		: AM PM					
12		: AM PM					
13		: AM PM					
14		: AM PM					
15		: AM PM					
16		: AM PM					
17		: AM PM					
18		: AM PM					
19		: AM PM					
20		: AM PM					
21		: AM PM					
22		: AM PM					
23		: AM PM					
24		: AM PM					
25		: AM PM					
26		: AM PM					
27		: AM PM					
28		: AM PM					

This patient diary is complete and accurate to the best of my knowledge.

Signature of parent/guardian: _____ Date: _____

This section for Local Study Site Use Only (not to be completed by parent/guardian):

Patient ID: _____ Institution Name: _____

Course #: _____ Dosing Height: ____ Dosing Weight: _____ BSA: _____

This patient diary has been verified for accuracy by (physician) _____ on ____/____/___

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