Phase II Study of Everolimus in Patients with Advanced Solid Malignancies with TSC1, TSC2, NF1, NF2, or STK11 Mutations

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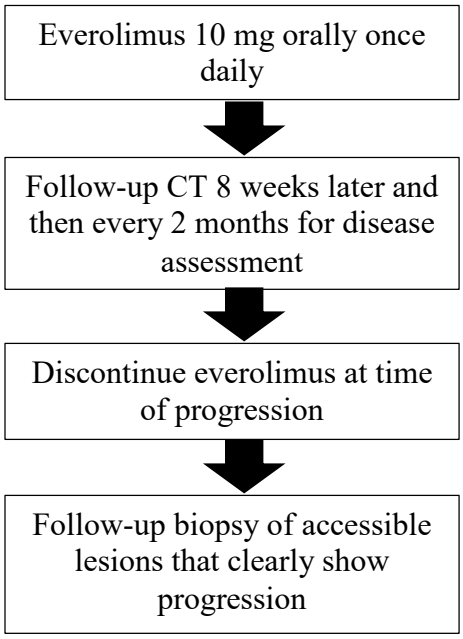
SCHEMA



Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ASH	American Society of Hematology
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
BM	Bone marrow
BMT	Bone marrow transplant
BUN	Blood urea nitrogen
CALGB	Cancer and Leukemia Group B
CBC	Complete blood count
CFR	Code of Federal Regulations
CMML	Chronic Myelomonocytic Leukemia
CNS	Central nervous system
CR	Complete remission
CRc	Cytogenetic complete remission
CRi	Complete remission incomplete
CRm	Morphologic complete remission
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLTs	Dose Limiting Toxicities
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
DSMC	Data Safety Monitoring Committee
DTIC	Dacarbazine
EC	Ethics Committee
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EE	Efficacy-Evaluable
EFS	Event free survival
EMEA	European Agency for Evaluation of Medicinal Products
FAB	French-American-British classification
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FWA	Federal wide assurance

GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor, filgrastim (Neupogen)
GM-CSF	Granulocyte/macrophage colony stimulating factor, sargramostim, (Leukine, Prokine)
HDACs	Histone deacetylases
HHS	Department of Health and Human Services'
HI	Hematologic improvement
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
ICH	International Conference on Harmonization
IFN	Interferon
IL-2	Interleukin-2
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous (i.v.)
IVRS	Interactive Voice Response System
IWG	International Working Group
LD	Longest diameter
LDH	Lactate dehydrogenase
LPS	lipopolysaccharide
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCL	Mantle cell lymphoma
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activity
MM	Multiple myeloma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCCN	National Cancer Center Network
NCI	National Cancer Institute
NIH	National Institutes of Health
NK	Natural killer cell
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protections
ORR	Overall response rate
OS	Overall survival
PB	Peripheral blood
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PI	Principal investigator

PR	Partial response (Partial remission)
PSA	Prostate-specific antigen
QASMC	Quality Assurance and Safety Monitoring Committee
RAEB	Refractory anemia with excess blasts
RAEB-t	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ringed sideroblasts
RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RFS	Relapse free survival
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SCT	Stem cell transplant
SD	Stable disease
TF	Treatment failure
TPP	Therapeutics Product Programme
TRAIL	TNF-related apoptosis-inducing ligand
TSH	Thyroid stimulating hormone
TTP	Time to progression
UPN	Unique patient number
US	Ultrasound
VEGF	Vascular endothelial growth factor
VPA	Valproic acid
WBC	White blood cell (count)
FCBP	Females of child bearing potential
WHO	World Health Organization

Table of Contents

1.0 BACKGROUND AND RATIONALE

1.1 The Mammalian Target of Rapamycin (mTOR) Pathway

Activation of the mammalian target of rapamycin (mTOR) pathway has been implicated in the development of several malignancies.[1,2] A member of the phosphatidylinositol 3-kinase (PI3K)-related family of kinases, mTOR is a 289-kDa protein serine/threonine kinase that was first identified as the cellular target of rapamycin and is involved in checkpoint regulation of the cell cycle regulation. Additionally, the mTOR pathway is responsible for upregulating downstream signaling of hypoxia inducible factor-1-α (HIF1-α) which promotes angiogenesis and cell proliferation.[3] mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, the rapamycin sensitive mTOR complex 1 (mTORC1), and rapamycin insensitive mTOR complex 2 (mTORC2). mTORC 1 is mainly activated via the PI3K pathway through AKT and the tuberous sclerosis complex (TSC1/TSC2). Activated AKT phosphorylates TSC2, which leads to dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. Another regulator of the mTOR pathway is NF1.

1.2 Everolimus

Everolimus is a novel oral derivative of rapamycin. At the cellular and molecular level, everolimus acts as a signal transduction inhibitor, and selectively inhibits mTOR. Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has been in development for patients with various malignancies since 2002. It has been demonstrated to have activity in several human solid tumor cell lines, as well as in mouse xenograft models.[4-7] Everolimus was first approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) in 2009. It recently received approval for use in patients with advanced pancreatic neuroendocrine tumors as well. The FDA approved dose of everolimus is 10 mg daily by mouth. Everolimus is extensively metabolized in the liver and eliminated by bile. It is a substrate of CYP3A4 and substrate and inhibitor of P-glycoprotein. It well tolerated, with the most common adverse reactions being stomatitis, fatigue, nausea, diarrhea. Grade 3-4 adverse reactions (≥2%) include infections, stomatitis, fatigue and pneumonitis. The most common laboratory abnormalities are anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia and increased creatinine.[8]

[redacted]

[10-12]

1.2.1 Overview of Everolimus

[redacted]

1.2.2 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 (Cohen et al 2005).

The main known functions of mTOR include the following (Bjornsti and Houghton 2004):

- 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 (Frattini 2005, Velho 2005);
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers (Goel et al 2004);
- 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.

[redacted]

[redacted]

1.3 Next Generation Sequencing

TSC1,TSC2, NF1 NF2, and STK11 mutational analysis will be performed as part of a larger panel of genomic testing to aid in treatment of patients with cancer as standard of care and will not be billed to Novartis. This screening will identify potential patients for this study. Provided they meet other eligibility criteria, they will be consented to participate in the study.

Genes to be sequenced include TSC1,TSC2, NF1, NF2 and STK11. The technology employed will permit detection of single nucleotide variants, small insertions, deletions, and complex indels, as well as amplifications and large deletions across the coding regions of all sequenced genes. Tumor-derived DNA obtained from formalin fixed, paraffin embedded tissue will serve as the source of input material for the assay. Sensitive and specific methods to call variants and other genomic alterations will be performed using a clinical grade data analysis pipeline including a software package allowing for interpretation and reporting of such findings.

1.4 Study Rationale

Cancer is a molecularly heterogeneous disease comprised of complex genomic alterations in common and overlapping pathways. Complicating the heterogeneous nature of cancer is the clonal evolution that occurs within a tumor [10]. The molecular landscape of the tumor at time of diagnosis may differ significantly from the molecular profile at the time of disease progression [11]. It is critical that tumor samples are obtained at the time of diagnosis and following disease progression. Key alterations in the tumor biology can be identified efficiently through use of routine next generation sequencing. It is important to identify predictive biomarkers for response to molecularly targeted agents; however, it is also important to investigate biomarkers that confer resistance to specific therapies. As an example, 10% of non small cell lung cancers (NCSLC) carry activating mutations in the epidermal growth factor receptor tyrosine kinase (EGFR TK).[12] Although tyrosine kinase inhibitors such as erlotinib have demonstrated response rates of approximately 70-90% [13,14], drug resistance eventually develops as a consequence of an emergence of a population of tumor cells harboring a new mutation in the EGFR TK domain or amplification in the MET oncogene [15]. As a result, clinical studies are underway targeting EGFR mutations in combination with MET inhibitors to target the genomic alterations that are occurring at the time of progression on an EGFR inhibitor. Using a similar model, mutations in the mTOR/PI3K pathway and potential mechanisms of resistance to everolimus can be identified using routine next generation sequencing at the time of diagnosis and at time of disease progression.

2.0 OBJECTIVES

2.1 Primary Objectives

To assess the response rate of patients with solid malignancies whose tumors carry mutations in TSC1, TSC2, NF1, NF2, or STK11 to everolimus.

2.2 Secondary Objectives

1. To correlate mutations in the mTOR pathway with therapeutic response to everolimus.
2. To investigate the genetic changes associated with disease progression following treatment with everolimus.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed diagnosis of advanced (metastatic, recurrent, or unresectable) cancer with mutations in any of the following genes: TSC1,TSC2, NF1, NF2 or STK11

2. Must have failed at least 1 standard of care systemic therapy for their malignancy.

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with CT scan, as $\geq$20 mm by chest x-ray, or $\geq$10 mm with calipers by clinical exam.

4. Prior therapy (chemotherapy, radiation therapy, and surgery) is allowed if completed at least 2 weeks prior to registration and if all treatment-related toxicities are resolved to $\leq$ CTCAE grade 1, with the exception of alopecia and hematologic values otherwise meeting the bone marrow function criteria specified below.

5. At least 18 years of age.

6. ECOG performance status $\leq$ 2 (see Appendix A).

7. Normal bone marrow and organ function as defined below:
   a. Leukocytes > 3,000/mcL
   b. Absolute neutrophil count > 1,500/mcL
   c. Platelets > 100,000/mcL
   d. Hemoglobin > 9.0 g/dL
   e. Total serum bilirubin $\leq$ 2.0 x IULN
   f. AST(SGOT)/ALT(SGPT) $\leq$ 2.5 x IULN ($\leq$ 5.0 x IULN in patients with liver metastases)

g. Serum creatinine ≤ 1.5 x IULN OR creatinine clearance > 45 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal
h. Fasting cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5 x IULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication

8. Able to swallow tablets.

9. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception (please refer to Section 5.4) during the study and for 8 weeks after. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

10. Male patients whose sexual partner(s) are women of childbearing potential must agree to use adequate contraception during the study and for 8 weeks after the end of treatment.

11. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable)

3.2 Exclusion Criteria

1. A history of other malignancy ≤ 3 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

2. Taking an investigational agent within 4 weeks of initiation of everolimus.

3. Symptomatic brain metastases. Known brain metastases are allowed if asymptomatic and previously treated.

4. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to everolimus or other agents used in the study.

5. Known impairment of GI function or GI disease that may significantly alter the absorption of oral everolimus.

6. Currently taking CYP3A4 inhibitors or inducers (such as the antiepileptic drugs phenytoin, carbamazepine, or phenobarbital; cyclosporine; grapefruit or its juice; Seville oranges; starfruit; or St. John's wort) (refer to Section 5.3).

7. Chronic treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

8. Received live attenuated vaccine within 1 week of start of everolimus (i.e. intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines).

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

10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure of NYHA class III or IV, active coronary artery disease, unstable angina pectoris, cardiac arrhythmia, myocardia infraction ≤ 6 months prior to start of everolimus, uncontrolled hypertension (systolic pressure > 150 mmHg or diastolic pressure > 90 mmHg), uncontrolled seizure disorder, liver disease such as cirrhosis, decompensated liver disease, active and chronic hepatitis, known severely impaired lung function (spirometry and DLCO 50% or less of normal and 02 saturation 88% or less at rest on room air), active bleeding diathesis, or psychiatric illness/social situations that would limit compliance with study requirements.

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

12. Known HIV-positivity on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with everolimus. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

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

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

1. Confirmation of patient eligibility

2. Registration of patient in the Siteman Cancer Center Oncore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

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

4.2 Patient Registration in the Siteman Cancer Center Oncore Database

All patients must be registered through the Siteman Cancer Center.

4.3 Assignment of UPN

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

5.0 TREATMENT PLAN

This is an open label, single-arm phase II trial focusing on the response rate of everolimus. The study treatment plan is as follows:

1. Everolimus 10 mg orally, once daily
2. Follow-up CT scan 8 weeks later and then every two months for disease assessment
3. Discontinue everolimus at the time of progression as defined by RECIST 1.1 criteria
4. Follow up biopsy (of accessible lesions that clearly showed progression)

5.1 Agent Administration

Everolimus is an oral drug which will be administered on an outpatient basis at a dose of 10 mg daily on a 28-day cycle. Patients should take everolimus at approximately the same time every day, either consistently with or consistently without food. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered. If vomiting occurs, no attempt should be made to replace the vomited dose. If a patient misses a dose, the patient should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Patients will be instructed to bring all unused tablets and their medication diary (see Appendix B) to each study visit for assessment of compliance.

5.2 Supportive Care Guidelines

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 stomatitis, rash, diarrhea, fatigue, infections, asthenia, nausea, peripheral edema, decreased appetite, headache, dysgeusia, epistaxis, mucosal inflammation, pneumonitis, weight decreased, vomiting, pruritus, cough, dyspnea, dry skin, nail disorder, and pyrexia. Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia).; increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases, creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

5.2.1 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 sepsis, 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.

Cases of pneumocystis jirovecii pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

5.2.2 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.

5.2.3 Management of hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

5.2.4 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment).

5.2.5 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

5.2.6 Management of stomatitis / oral mucositis / mouth ulcers

Severity	Everolimus Dose Adjustment and Management Recommendations
Grade 1 (Minimal symtpoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash severaltimes a day.
Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine,butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol)with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine,butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*
Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue everolimus and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen 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. The suggested paradigm for treatment of stomatitis/oral mucositis/mouth ulcers is as follows:

1. For mild toxicity (grade 1), no dose adjustment required. Manage with 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. These agents should be avoided.
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.

5.2.7 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 (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

5.2.8 Management of hyperlipidemia and hyperglycemia

Severity	Everolimus Dose Adjustment and Management Recommendations
Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
Grade 3	Temporary dose interruption. Re-initiate everolimus at lower dose. Manage with appropriate medical therapy and monitor.
Grade 4	Discontinue everolimus and treat with appropriate medical therapy.

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 a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g. atorvastatin, pravastatin, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on everolimus.

5.2.9 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. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. 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.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt everolimus until resolution to less than or equal to grade 1. Everolimus may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of everolimus. For cases of grade 4 non-infectious pneumonitis, everolimus therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered. The two compounds studied most extensively for prophylaxis against PJP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

If non-infectious pneumonitis develops, the guidelines in the table below should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Management of non-infectious pneumonitis

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interering with Activities of Daily Living)	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 (Symptomatic, Interfering with Activities of Daily Living. O_2 indicated	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 (approximately 50% lower than the dose previously administered depending on individual clinical circumstances) Discontinue Everolimus if failure to recover within ≤ 28 days.If toxicity recurs at Grade 3, consider discontinuation
Grade 4 (Life-threatening, ventlatory support indicated)	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.

5.2.10 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). 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 (Loomba 2008). 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.

Monitoring and prophylactic treatment for hepatitis B reactivation
The table below provides detail of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

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 the table below.

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 3.0 - 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.

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 the table below.

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 3.0 - 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).

5.3 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.

5.3.1 Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

Co-administration with strong inhibitors of CYP3A4 or PgP should be avoided; and may cause increased everolimus concentrations. For a current table of Substrates, Inhibitors and Inducers please access the following website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

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 by approximately 50%. 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.
    - **TSC with SEGA:** Everolimus trough concentrations should be assessed approximately 2 weeks after the addition of a moderate CYP3A4/PgP inhibitor. If the inhibitor is discontinued the everolimus dose should be returned to the dose used prior to initiation of the inhibitor and the everolimus trough concentration should be re-assessed approximately 2 weeks later.
- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of everolimus (based on pharmacokinetic data), using increments of 5 mg or less. This dose of everolimus is predicted to adjust the 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, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.
    - **TSC with SEGA** Patients receiving concomitant strong CYP3A4 inducers (e.g., the enzyme inducing antiepileptic drugs carbamazepine, phenobarbital, and phenytoin) may require an increased everolimus dose to attain trough concentrations of 3 to 15 ng/mL. Double the daily dose of everolimus and assess tolerability. Assess the everolimus trough level two weeks after doubling the dose. Further adjust the dose if necessary to maintain the trough within the 3 to 15 ng/mL range. If the strong inducer is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4 inducer and the everolimus trough concentrations should be assessed approximately 2 weeks later.
- 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 the tables below listing relevant inducers and inhibitors of CYP3A and relevant substrates, inducers, and inhibitors of PgP.

5.3.2 Everolimus and drugs influencing CYP3A4 enzyme

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Refer to Table 6-2 in section 6 for a comprehensive list of inducers and inhibitors of CYP3A4 and Table 6-3]for a list of relevant substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins). Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ and the tables below.

Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
Moderate inducers: bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir
Weak inducers: amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine

Inhibitors
Strong inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole **Moderate inhibitors:** Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil

Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 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.

5.3.3 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. For pediatric patients with SEGA that do not require immediate treatment, complete the recommended childhood series of live virus vaccinations prior to the start of therapy according to local treatment guidelines. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5.4 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of everolimus.

Female and male patients (along with their female partners) are required to use highly effective contraception during participation in the study and for 8 weeks following the last dose of everolimus. Highly effective contraception methods include a combination of any two of the following:

- Use of oral, injected, or implanted hormonal methods of contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods such as condom or occlusive cap (diaphragm or cervical/vault cap) with spermicidal foam/gel/film/cream/vaginal suppository
- Total abstinence
- Male/female sterilization

If a patient is suspected to be pregnant, everolimus should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 8 weeks after the last dose of everolimus, the investigator must be notified in order to facilitate outcome follow-up.

5.5 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue indefinitely until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.6 Duration of Follow-up

Patients will be followed for 30 days after the last dose of everolimus or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

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. Details of study treatment schedule adjustments and dose levels are provided below.

Dose level	Dose and schedule
0 (starting dose)	10 mg QD
-1	5 mg QD
-2	2.5 mg QD

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients who need an additional dose reduction will be required to discontinue everolimus.

Please refer to Section 5.3.1 for alternative dose modifications relating to concomitant medications.

The tables below list the dosing guidelines for everolimus-related non-hematologic and hematologic toxicities.

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption (with or without dose reduction) of everolimus therapy. If dose reduction is required, the suggested dose is approximately 50% lower than the daily dose previously administered.

The proceeding sections summarize recommendations for dose interruption, reduction, or discontinuation of everolimus in the management of ADRs. General management recommendations are also provided as applicable. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Dosing guidelines for Everolimus-related non-hematologic toxicities

Toxicity	**Action**
Non-Infectious Pneumonitis	See Section 5.2.9
Reactivation of HBV or HCV flare	See Section 5.2.10
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 (see Section 5.2.8)	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 2.5 mg daily. Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation
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	

Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	Action
Grade 3 thrombocytopenia, neutropenia, or anemia	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, neutropenia, or anemia	Interrupt everolimus until recovery to grade ≤ 1. Then reintroduce everolimus at one dose level lower, if available.
Febrile neutropenia	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
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 5 mg every other day (2.5 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

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

Novartis Pharmaceuticals requires that every SAE regardless of suspected causality that occurs after the patient has provided consent and after protocol-specified procedures have begun be reported as outlined in Section 7.4.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the

terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

7.1.5 Unanticipated Problems

Definition:

- 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;
- 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.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as

reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to Novartis

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 (e.g., placebo run-in, washout period, double-blind treatment, etc.) 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, not related, labeled (expected) and unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

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, whether the blind was broken or not (if applicable), 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.

7.4.1 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.

7.5 Timeframe for Reporting Required Events

Adverse events will be tracked for 30 days following the last day of study treatment.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.4 Supplier(s)

Everolimus will be provided by Novartis Pharmaceuticals.

8.1.5 Dosage Form and Preparation

Everolimus is formulated as tablets for oral administration of 2.5 mg, 5 mg, and 10 mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as the drug is both hygroscopic and light-sensitive.

8.1.6 Storage and Stability

Store at 25°C (77°F); excursions permitted between 15°C-30°C (59°-85°F). Store in the original container. Protect from light and moisture.

8.1.7 Administration

Everolimus is an oral drug which will be administered on an outpatient basis at a dose of 10 mg daily.

8.1.8 Special Handling Instructions

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of tablets. Wash hands thoroughly before and after preparation of either suspension.

9.0 CORRELATIVE STUDIES

9.1 Archived Tumor Tissue

If mutational testing has not already been performed, next generation sequencing and screening for mutations in TSC1, TSC2, NF1, NF2 and STK11 will be performed on archived formalin-fixed paraffin-embedded (FFPE) tumor tissue as part of the patient's routine care at any qualifying CLIA-certified laboratory that reports clinical next-generation sequencing of these genes. If the archival tissue does not have adequate viable cells for next generation sequencing to be performed, a fresh biopsy may be done prior to initiation of treatment. This is being done as part of routine care, and only patients who show a mutation in TSC1, TSC2, NF1, NF2 and STK11 may enroll to the study.

9.2 Fresh Tumor Biopsy

9.2.1 Collection of Specimen(s)

Accessible lesions that clearly show progression will be biopsied using standard of care parameters at the time of progression.

9.2.2 Handling of Specimen(s)

Collect and place in normal saline for delivery to the Siteman Cancer Center Tissue Procurement Core.

10.0 STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done no more than 28 days prior to the start of the protocol therapy. All visits have a window of +/- 3 days.

	Screening	Day 1 of each cycle	End of every even-numbered cycle	End of treatment	Follow-up[4]
Informed consent	X				
H&P, ECOG PS, weight	X			X	
CBC	X	X[6]		X	
CMP	X	X[6]		X	
Hepatitis B and C testing	X				
Lipid panel[5]	X				
INR	X				
HbA1c	X				
Pregnancy test[1]	X				
Standard of care imaging	X		X	X	
Archival tissue for TSC1, TSC2, NF1, NF2 and STK11 mutations[7]	X				
Fresh tissue for research purposes				X[3]	
Everolimus		X ---------- X[2]			
Adverse event assessment	X ---------- X				
Concomitant medications	X ---------- X				

1. Women of childbearing potential only
2. To be taken PO QD
3. At time of progression, biopsy of accessible lesions showing progression will be done
4. 30 days post-EOT
5. Should be performed periodically during treatment at the discretion of the treating physician
6. If screening labs are performed within 3 days prior to C1D1, the labs do not need to be repeated
7. Mutation testing can be done at any point prior to study enrollment

11.0 DATA SUBMISSION SCHEDULE

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

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Tumor Biopsy Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form Concomitant Medications Form	Continuous
Treatment Summary Form Tumor Biopsy Form	Completion of treatment
Follow Up Form	30 days after end of treatment
Tumor Measurement Form	Baseline, end of every even numbered cycles, and end of treatment
Adverse Events Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where

recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

12.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** 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.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

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

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

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

13.0 DATA AND SAFETY MONITORING

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

The Principal Investigator will review all patient data at least monthly and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

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

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design

This is an open label, single-arm phase II trial focusing on the response rate of the therapeutic agent. Since this is a study in patients with specifically targeted mutations, a rather big treatment effect size is expected. Based on historical data, we assume a null hypothesis of an overall response rate of <1% in this setting.[9] We hypothesize that an overall response rate of 30% or higher warrants further investigation. A total of N=12 patients will be enrolled for this study, based on the exact single-stage design with 85% power at a 1-sided 0.05 significance level (using *ph2single* function from library *clinfun* in the R package). If 2 or more responders are observed out of these 12 patients, we would conclude that preliminary evidence for efficacy exists and that further investigation of the treatment is warranted.

14.2 Data Analysis

The primary endpoint will be to describe the response rate using RECIST 1.1. Response rate will be defined as complete response (disappearance of all target lesion) plus partial response (a least a 30% decrease in the sum of diameters of target lesions). Secondary endpoint will be to further evaluate molecular markers of response or resistance using exome sequencing and transcriptome sequencing when feasible.

Demographic and clinical characteristics of the sample, as well as response, and toxicity by grade will be summarized using descriptive statistics. The overall response rate and its 90% confidence interval will be estimated. If possible, permutation tests will also be performed to compare the differences of secondary endpoints between responders and non-responders. The distribution associated with no difference (the null distribution) can be identified using the data in hand. If there is no difference between the values seen in responders and those in non-responders, then, for this purpose, it does not matter whether a given patient is labeled as a responder or a nonresponder. So we can randomly shuffle the response labels and calculate the test statistic from the shuffled data. If this procedure is repeated 10,000 times, the resulting 10,000 test statistics provide an accurate representation of the null distribution. The observed test statistic, based on patients assigned to the correct response group, is then compared to the null distribution. If the observed test statistic is unusually large or small, so very few values from the null distribution are larger or smaller than the observed test statistic, then the observed difference between responders and non-responders is unlikely if the null hypothesis were correct. In that case, we can reject the null hypothesis of no difference and conclude that there is a true difference between responders and non-responders. Then the null distribution

of the test statistics will be generated by simulating 10,000 datasets where the status of response was randomly shuffled. In order to quantify the extent to which the observed test statistic is "unusual," a permutation test generates a p-value, which is equal to the proportion of test statistics from the label-shuffled samples that exceed the observed test statistics.

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APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: Everolimus

Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take ___ mg (___pills) of everolimus at approximately the same time every day, either consistently with or consistently without food. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the pills whole and do not chew them.
2. Record the date, the number of pills taken, and when you took them.
3. If you forgot to take your dose before 6:00PM, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Bring your unused pills and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?	# of pills taken	Comments
1				
2				
3				
4				
5				
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11				
12				
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