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Title: A Phase II trial of everolimus for cancer patients with inactivating mutations in TSC1 or TSC2 or activating MTOR mutations

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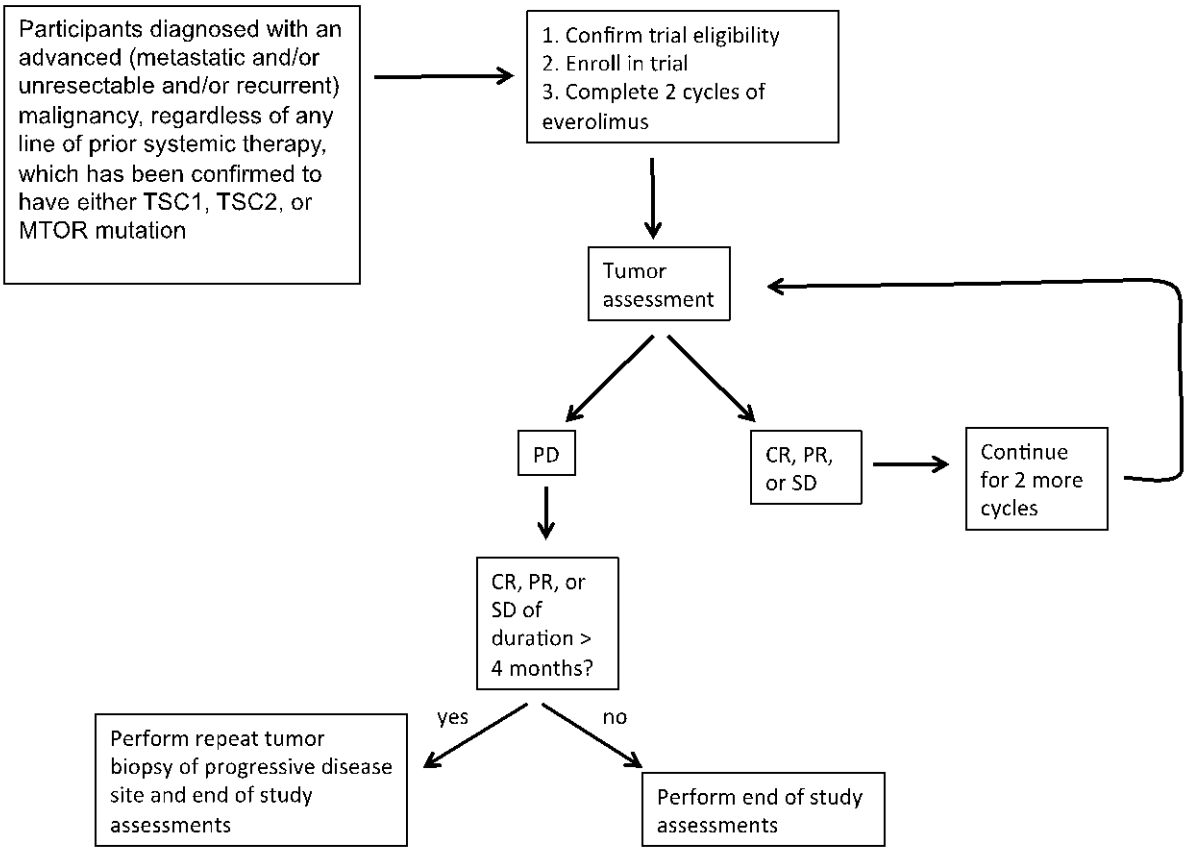
Agent(s): Everolimus

Study Exempt from IND Requirements per 21 CFR 312.2(b).

SCHEMA



Patients will stay on study as long as they do not progress. Tumor assessments will be performed after every 2 cycles for as long as they are on study.

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1. OBJECTIVES

1.1 Study Design

This is a single-arm non-randomized phase II study evaluating the mTOR inhibitor everolimus in cancer patients who have documented inactivating mutations in TSC1, TSC2, or activating MTOR mutations in their cancers.

1.2 Primary Objectives

1) Evaluate the clinical benefit of everolimus, defined as objective response (RECIST 1.1) in patients with tumors that have been confirmed prior to study entry to have TSC1, TSC2, or MTOR mutations.

1.3 Secondary Objectives

1) Perform immunohistochemical analysis and whole exome sequencing on all study patients to examine correlations between other genetic and genomic events and response.
2) Assess duration of response, progression-free survival, overall survival, and toxicity.

2. BACKGROUND

2.1 Study Agent(s)

2.1.1 Everolimus

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

Everolimus was developed in oncology as Afinitor® and was approved for advanced renal cell carcinoma (RCC) in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC. Afinitor® was approved for “progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease” in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore, in 2012, Afinitor® received

approval for the treatment of adult patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

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

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

In addition, healthy volunteer subjects and non-oncology subjects with hepatic impairment have participated in clinical pharmacology studies.

Mechanism of Action:

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex known as mTORC1. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (1).

Everolimus is being investigated as an anticancer agent based on its potential to act directly on the tumor cells by inhibiting tumor cell growth and proliferation; and indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Rationale for Starting Dose

Everolimus has been approved for the treatment of ER positive/HER2 negative breast cancer following failure of aromatase inhibitors, for advanced RCC, for pancreatic neuroendocrine tumors and renal angiomyolipoma at a dose of 10 mg daily. This dose will be administered in this study.

Safety Profile

As of September 30th 2011, 18,730 cancer patients have been treated with everolimus. The frequency and severity of side effects are available from the prescribing information pamphlet for physicians:

http://www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf

2.2 Study Disease/Rationale for the Study

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 protein complex made of the gene products of the two genes which cause tuberous sclerosis complex (TSC1/TSC2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in dysregulation of mTOR. Abnormal functioning of various components of this signaling pathway contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development (2).

The main known functions of mTOR include acting as a sensor of mitogens, growth factors and energy and nutrient levels; and it facilitates cell-cycle progression from G1-S phase in appropriate growth conditions (3).

The PI3K/mTOR pathway 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 and other cancers (4, 5). The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers and many other cancer types (6). 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.

Several clinical studies have now been reported in which everolimus has shown clinical benefit for patients with cancers with mutations in TSC1 or TSC2. Randomized clinical trials in patients with the genetic disorder Tuberous Sclerosis Complex (TSC) who have tumors in the brain, subependymal giant cell astrocytoma, or renal angiomyolipoma, have shown benefit in response to everolimus treatment (7, 8). PEComas, a sarcoma related to angiomyolipoma, but occurring in non-TSC patients and usually due to mutations in TSC2, have also shown benefit including sustained complete responses while on everolimus (9, 10). Finally, a recent report described a clinical trial of everolimus for bladder cancer, in which one patient had a sustained complete clinical response lasting over 2 years (11). That patient was shown to have a TSC1 inactivating mutation in her cancer. Notably, other bladder cancer patients on that trial whose cancers also had mutations in TSC1 had transient minor responses. However, the majority of patients on the trial had no mutations in TSC1, and showed progressive disease. Both TSC1 and TSC2 mutations and mTOR activating mutations have been identified in a set of 6 extreme responders to Everolimus out of 300 patients with renal cell carcinoma treated at Memorial Sloan Kettering (12). Furthermore, an activating MTOR mutation has been associated with exceptional response to treatment

in a bladder cancer patient (13), and multiple, relatively common, activating MTOR mutations have been defined through in vitro studies (14).

We hypothesize that due to the positioning of TSC1/TSC2 as a key regulator of mTORC1, that all cancers with inactivating mutations in TSC1 or TSC2 will have sensitivity to everolimus. The extent of sensitivity will likely depend on other genomic events present in these cancers, tissue type, and other unknown factors. Furthermore, we similarly hypothesize that cancers bearing MTOR activating mutations will also have sensitivity to everolimus.

2.3 Correlative Studies Background

As described above, the TSC1/TSC2 protein complex functions as a key regulator of mTORC1 activity, and hence mutation in either gene results in strong activation of mTORC1, both in vivo (mouse tumor models, human cancers (e.g. PEComa)) and in vitro (multiple cell lines). Nonetheless, human cancers are often subject to numerous mutations and genomic copy number changes throughout the genome. In the publication in which Everolimus was described to cause a complete sustained clinical response in a patient with metastatic bladder cancer, the responding patient's cancer also had a mutation in NF2 and other genes. We hypothesize that other genetic and genomic events affect sensitivity to Everolimus, and hence wish to perform whole exome sequencing to identify both mutational events and genome-wide copy number changes (amplifications and deletions) on cancer samples from patients on this trial. Furthermore, in responding patients who subsequently progress, we will also require repeat biopsy to permit genetic studies to examine the mechanism of resistance, as long as this can be performed without medical risk. In addition, we will prepare cancer cell lines from these patients using either the patient-derived xenograft system, or through direct establishment of a cell line using a feeder layer.

3. PARTICIPANT SELECTION

This study will enroll 30 patients with inactivating mutations in TSC1 or TSC2, or activating mTOR mutations.

3.1 Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

3.1.1 Participants must have histologically confirmed advanced malignancy that is metastatic and/or unresectable and/or recurrent with confirmed inactivating mutations in TSC1 or TSC2 or activating MTOR mutations, identified in any

CLIA-certified laboratory. All genetic findings must be reviewed by the study PI, Dr. David Kwiatkowski, prior to study entry.
Biopsy of a primary or metastatic lesion must have been performed within the past two years. Sufficient pathologic material must be available to enable whole exome sequencing at the time of study entry. Patients with biopsy samples older than 2 years must undergo a fresh tumor biopsy or should receive approval for enrollment from the Principal investigator.

3.1.2 Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 10 for the evaluation of measurable disease.

3.1.3 Participants may have received any number of prior therapies, from 0 to > 10. Prior treatment with PI3-kinase or mTOR inhibitors is not permitted, unless they were given as adjuvant therapy without undue toxicity, and without suggestion of resistance to therapy.

3.1.4 Age ≥ 18 years.

3.1.5 ECOG performance status ≤2 (see Appendix A).

3.1.6 Participants must have normal organ and marrow function as defined below:

- Leukocytes ≥ 3,000/mcL
- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 9.0 gr/dL
- total bilirubin ≤ 1.5 X the institutional upper limit of normal (ULN)
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal. Patients with confirmed liver metastases are permitted to have AST/ALT at levels ≤ 5 X the institutional upper limit of normal (ULN)
- creatinine ≤ 1.5 X the institutional upper limit of normal (ULN)
- Total cholesterol < 300 mg/dL
- Triglycerides < 250 mg/dL

3.1.7 The effects of everolimus on the developing human fetus are unknown. For this reason and because anti-neoplastic agents are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect

she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign a written informed consent document.

3.1.9 Participants who achieve either a partial response or stable disease ≥ 4 months must agree to undergo a tumor biopsy, if safe and feasible, at the time of progressive disease while on study drug everolimus.

3.2 Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study.

3.2.1 Participants who have had any of the following:

3.2.1.1 Chemotherapy in the previous 2 weeks (6 weeks for nitrosoureas or mitomycin C)

3.2.1.2 Radiotherapy within 3 weeks

3.2.1.3 Investigational agents within 3 weeks prior to entering the study

3.2.1.4 Patients who have not recovered from significant (in the opinion of the investigator) adverse events due to previous agents administered.

3.2.2 Child-Pugh B or C hepatic impairment. Patients with a history of hepatitis or significant exposure risk should be tested for hepatitis B and C with serologic markers: HBsAg, HBs Ab, HBcoreIgG Ab, and HCV Ab. Patients with active hepatitis B or C are excluded.

3.2.3 Participants may not be receiving any other research study agents.

3.2.4 Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases. Asymptomatic or treated brain metastases are acceptable.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to everolimus.

3.2.6 A list of prohibited medications on study are listed in Section 5.5

3.2.7 Chronic treatment with corticosteroids or other immunosuppressive therapy

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

3.2.9 Pregnant women are excluded from this study because everolimus has the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with everolimus, breastfeeding should be discontinued if the mother is treated with everolimus. These potential risks may also apply to other agents used in this study.

3.2.10 Individuals with a recent history of a different malignancy are ineligible except for the following circumstances: 1) Individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years OR are deemed by the investigator to be at low risk for recurrence of that malignancy; 2) Individuals with the following cancers are eligible if diagnosed and treated within the past 3 years: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

3.2.11 Individuals with known HIV infection are excluded from this study as combination antiretroviral therapy could potentially result in significant pharmacokinetic interactions with everolimus. In addition, these individuals are at increased risk of lethal infections due to the immunosuppressive effects of mTOR inhibition.

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

3.2.13 Uncontrolled diabetes mellitus: HbA1c must be < 8% or there must be documentation that control has been good for the week prior to study entry, with daily morning glucoses at < 150 mg/dl. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.

3.3 Inclusion of Women, Minorities and Other Underrepresented Populations

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Office of Data Quality (ODQ) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the ODQ Registrar of registration cancellations as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

The ODQ registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the ODQ registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the ODQ protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. **To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.**
- Fax the eligibility checklist(s) and all pages of the consent form(s) to the ODQ at 617-632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.
- The ODQ Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.
- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

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4.3 General Guidelines for Other Participating Institutions

Eligible participants will be entered on study centrally at the DFCI by staff of the coordinating center. Following registration, participants should begin protocol therapy within 5 days. * Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The staff at the coordinating center should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Participating Institutions

To register a participant on this study, please refer to Appendix C, Data and Safety Monitoring Plan (DSMP) Section 3.7.

5. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for everolimus are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modification). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy. As this is a non-randomized trial, all trial subjects will receive everolimus.

If a patient is deriving clinical benefit, they may continue on treatment beyond progressive disease with PI approval.

5.1 Dosing Plan

The study drug Everolimus will be self-administered. The investigator will instruct the patient to take the study drug exactly as specified in the protocol. Everolimus will be administered orally as once daily dose of 10 mg (one 10mg tablet) continuously from study day 1 until progression of disease or unacceptable toxicity. Patients will be instructed to take Everolimus in the morning, at the same time each day, and to keep a pill diary. A treatment cycle is defined as 28 days (4 weeks).

It is recommended that Everolimus is taken in the morning, one hour prior to breakfast. Dietary habits around the time of Everolimus intake should be as consistent as possible throughout the study. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered.

Doses of everolimus may be administered with or without food, whatever is most convenient for the participants. However, dosing with or without food must be consistent throughout the course of the study.

If vomiting occurs, no attempt should be made to replace the vomited dose.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

Everolimus will be provided by Novartis. Everolimus is formulated as tablets for oral administration of 5mg and 10 mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Typically, patients will be given a 4-week supply; however, after cycle 2 it may be an 8-week supply at the discretion of the investigator.

5.2 Screening Criteria

All subjects or their legally acceptable representative and the person who conducted the informed consent discussion must personally sign and date the consent form before any study-specific screening procedures are performed. Procedures that have been performed before consent was obtained as part of routine care are not considered study-specific procedures.

Medical history information to be collected during screening must date back to the original diagnosis of cancer. If a subject is referred to the study center, a copy of all applicable reports and histological or cytological evidence, confirming the diagnosis must be provided to the study center before enrollment. Copies of recent (i.e., within the past 6 months) radiographic images confirming disease progression by modified RECIST should be provided to the study center.

All subjects who have signed the IRB approved consent form must be registered as a screened subject. At the time of registration, the subject will receive a unique 2 digit subject identification number. This number will be used to identify the subject throughout the study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire study.

All screening tests and procedures must be performed and the results available within a maximum of 14 days before study day 1 unless otherwise noted.

Subjects who do not meet eligibility criteria within the 14 day screening period will not be eligible for enrollment. However, subjects may be re-screened up to 2 additional times at the discretion of the investigator. The subject must be re-consented if more than 28 days have elapsed since the date of last informed consent.

The following screening assessments must be performed:

- Review of inclusion and exclusion criteria
- Medical history review, documentation of diagnosis and previous treatment.
- Physical examination, ECOG performance status, blood pressure, respiratory rate, resting pulse, temperature, height and weight.
- CT scans (contrast-enhanced) or MRI scan (contrast-enhanced) of areas of known disease and that are of acceptable quality as baseline study within 30 days prior to study day 1.

Laboratory assessment consisting of

- Hematology
- Chemistry
- Urinalysis
- beta HCG pregnancy test for women of child-bearing potential

5.3 Pretreatment Criteria

The first dose of Everolimus may be administered on the same day as enrollment but no more than 10 business days after enrollment. The treatment period begins on the first day of treatment with Everolimus.

If a subject is unable to come into the clinic for a required study visit or if unforeseen events occur, the visit procedures may be performed within a one week time frame.

The following assessments will be performed at each clinic visit according to table 3.4 throughout the treatment period:

- Physical examination,
- ECOG performance status,
- Blood pressure, respiratory rate, resting pulse, temperature, and weight.
- Laboratory evaluations: If patients have met trial eligibility within the previous 72 hours, no specific criteria will need required in order to initiate the protocol unless, in the investigator's opinion, significant medical issues arise which would contraindicate starting the study medications. If patients have completed entry criteria >72 hours prior to cycle 1 day 1, laboratory values on cycle 1 day 1 should be repeated to confirm all eligibility criteria are met.
- CT scans (contrast-enhanced) or MRI scan (contrast-enhanced) or PET-CT scan of areas of known disease every 8 weeks with a 5 business-day time window in case unforeseen events occur. Evaluation according to RECIST criteria compared to previous scan.
- beta HCG pregnancy test for women of child-bearing potential

Documentation of all adverse events will occur at each clinic visit and at any other time point when necessary. There are no specific criteria for the initiation of a given cycle except for the ones indicated in the dose modification tables 6-2, 6-3 & 6-4. Study subjects may commence with treatment if, in the opinion of the investigator and based on the guidance of Section 6, it is safe for the participant to do so.

5.4 Agent Administration

Everolimus will be administered orally daily, either at the starting dose of 10 mg, or at a lower dose based on guidance in Section 6.

5.5 General Concomitant Medication and Supportive Care Guidelines

Any new medications that patients might start taking while on study need to be reported to the study MD first before they start taking it. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The following restrictions apply during the entire duration of the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. The only exception is that treatment with hormonal agents for either prostate or breast cancer may be continued (not added) during this study. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events, if this is thought to be appropriate.
- Concurrent administration of Everolimus and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of Everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with systemic steroids or another immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with Everolimus.

Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with Everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The co-administration of Everolimus and oral anticoagulants is possible but should be subject to verification of coagulation (INR) once steady state is reached (after one week's treatment).

A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

Please refer to Table 5-1 listing relevant inducers and inhibitors of CYP3A and Table 5.2 for a list of relevant substrates, inducers, and inhibitors of PgP.

Table 5-1 clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

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

Table 5-2 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

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

Vaccinations

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

5.6 Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue forever or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from treatment but is willing to be followed,
- Participants decides to withdraw consent from the study, or
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.

5.7 Duration of Follow Up

Participants will be followed until death after removal from treatment. This follow-up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3 months.

5.8 Criteria for Removal from Study

Participants will be removed from treatment when any of the criteria listed in Section 5.6 applies. The reason for discontinuation of treatment and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator.

6. EXPECTED TOXICITIES AND DOSING 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 in table 6-1:

Table 6-1 Study treatment schedule adjustments and dose levels

Dose level	**Dose and schedule**
0 (starting dose)	**10 mg daily**
-1	**5 mg daily**
-2	**5 mg every other day**

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.

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE v4.0) which is identified and located on the CTEP website at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants

continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

6.1 Anticipated Toxicities

A list of the adverse events and potential risks associated with Everolimus appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

Adverse Reactions Significant:
>10%:

Cardiovascular: Peripheral edema (4% to 45%), hypertension (4% to 30%; hypertensive crisis: 1%)

Central nervous system: Fatigue (7% to 45%), fever (15% to 32%), headache (18% to 30%), seizure (5% to 29%), anxiety/aggression/behavioral disturbance (SEGA: 21%), insomnia (6% to 17%), dizziness (7% to 14%)

Dermatologic: Rash (18% to 59%), acneiform dermatitis (3% to 25%), nail disorders (5% to 22%), acne (3% to 22%), cellulitis (SEGA: 29%), pruritus (13% to 21%), dry skin (9% to 18%), contact dermatitis (14%), excoriation (14%)

Endocrine & metabolic: Hypercholesterolemia (17% to 85%), hyperglycemia (12% to 75%; grades 3/4: <1% to 17%), hypertriglyceridemia (≤73%), bicarbonate decreased (≤56%), hypophosphatemia (9% to 49%), hypocalcemia (17% to 37%), albumin decreased (≤33%), hypoglycemia (≤32%), hypokalemia (12% to 29%), hyperlipidemia (renal transplant: 21%), hyperkalemia (renal transplant: 18%), amenorrhea (≤17%), hyponatremia (≤16%), dyslipidemia (renal transplant: 15%), hypomagnesemia (renal transplant: 14%)

Gastrointestinal: Stomatitis (oncology uses: 44% to 86%; grade 3: 4% to 9%; grade 4: <1%; renal transplant: 8%), diarrhea (14% to 50%; grade 3: ≤5%; grade 4: <1%), constipation (10% to 38%), abdominal pain (3% to 36%), nausea (8% to 32%: grade 3: ≤2%; grade 4: <1%), appetite decreased (6% to 30%), anorexia (1% to 30%), vomiting (15% to 29%; grade 3: ≤2%; grade 4: <1%), weight loss (9% to 28%), taste alteration (1% to 22%), gastroenteritis (1% to 18%), xerostomia (8% to 11%)

Genitourinary: Urinary tract infection (5% to 22%), dysuria (renal transplant: 11%)

Hematologic: Anemia (26% to 92%; grades 3/4: ≤15%; grade 4: <1%), PTT increased (SEGA: 72%), leukopenia (oncology uses: 26% to 58%; renal transplant 3%), lymphocytopenia (20% to 54%; grades 3/4: ≤18%), thrombocytopenia (19% to 54%; grade 3: ≤3%; renal transplant <10%), neutropenia (14% to 46%; grades 3/4: ≤9%)

Hepatic: AST increased (23% to 89%; grade 3: ≤4%; grade 4: <1%), alkaline phosphatase increased (32% to 74%), ALT increased (18% to 51%; grade 3: ≤4%; grade 4: <1%)

Neuromuscular & skeletal: Weakness (13% to 33%), arthralgia (≤20%), back pain (11% to 15%), limb pain (8% to 14%)
Otic: Otitis (6% to 36%)

Renal: Creatinine increased (11% to 50%), hematuria (renal transplant: 12%)

Respiratory: Upper respiratory infection (11% to 82%), sinusitis (3% to 39%), cough (7% to 30%), dyspnea (20% to 24%; grade 3: 2% to 6%; grade 4: ≤1%), epistaxis (≤22%), pneumonitis (includes alveolitis, interstitial lung disease, lung infiltrate, pulmonary alveolar hemorrhage, pulmonary toxicity; 1% to 19%; grade 3: 3% to 4%; grade 4: <1%), nasal congestion (14%), rhinitis (14%), pharyngitis (4% to 11%)

Miscellaneous: Infection (13% to 62%; grade 3: 4% to 7%; grade 4: 1% to 3%)

1% to 10%:

Cardiovascular: Chest pain (5%), tachycardia (3%), heart failure (1%), angina, atrial fibrillation, chest discomfort, deep vein thrombosis, edema (generalized), hypotension, palpitation, syncope

Central nervous system: Depression (5%), migraine (5%), chills (4%), agitation, hallucination, hemiparesis, hypesthesia, malaise, somnolence

Dermatologic: Eczema (10%), alopecia (≤10%), palmar-plantar erythrodysesthesia syndrome ([hand-foot syndrome] 5%), papule (5%), erythema 4%, onychoclasis (4%), pityriasis rosea (4%), skin lesions (4%), hirsutism, incision complications, hyperhydrosis, hypertrichosis

Endocrine & metabolic: Menorrhagia (6% to 10%), menstrual irregularities (6% to 10%), diabetes mellitus (exacerbation: 2%; new-onset: <10%), dysmenorrhea (6%), metrorrhagia (6%), cushingoid syndrome, dehydration, gout, hypercalcemia, hyperparathyroidism, hyperphosphatemia, hyperuricemia, iron deficiency, vitamin B12 deficiency

Gastrointestinal: Gastritis (7%), hemorrhoids (5%), dyspepsia (4%), dysphagia (4%), ageusia (1%), abdominal distention, epigastric discomfort, flatulence, gastroesophageal reflux, gingival hypertrophy, hematemesis, ileus, peritonitis

Genitourinary: Vaginal hemorrhage (8%), bladder spasm, erectile dysfunction, ovarian cysts, pollakiuria, polyuria, pyuria, scrotal edema, urinary retention, urinary urgency

Hematologic: Hemorrhage (3%), leukocytosis, lymphadenopathy, thrombocythemia

Hepatic: Bilirubin increased (3% to 10%; grades 3/4: ≤1%)

Neuromuscular & skeletal: Muscle spasm (≤10%), tremor (8%), paresthesia (5%), jaw pain (3%), joint swelling, musculoskeletal pain, myalgia, osteonecrosis, osteopenia, osteoporosis, spondylitis

Ocular: Eyelid edema (4%), ocular hyperemia (4%), conjunctivitis (2%), blurred vision, cataract
Renal: Renal failure (3%), BUN increased, hydronephrosis, interstitial nephritis, proteinuria, renal artery thrombosis, renal impairment

Respiratory: Pleural effusion (7%), nasopharyngitis (6%), pneumonia (6%), bronchitis (4%), pharyngolaryngeal pain (4%), rhinorrhea (3%), atelectasis, nasal congestion, pulmonary edema, sinus congestion, wheezing

Miscellaneous: Hypersensitivity (3%; includes anaphylaxis, dyspnea, flushing, chest pain, angioedema), BK virus infection, candidiasis, night sweats

<1% (Limited to important or life-threatening):

Aspergillosis, azoospermia, cardiac arrest, fluid accumulation, graft thrombosis, hepatic cholestasis, hepatitis B reactivation, lymphoma, oligospermia, pancreatitis, pancytopenia, polyoma virus infection (BK virus), progressive multiple leukoencephalopathy (PML), pulmonary embolism, respiratory distress, sepsis, skin cancer, synovitis (severe), testosterone levels decreased, thrombotic microangiopathy/thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TMA/TTP/HUS), wound healing impaired

6.2 Toxicity Management

Table 6-2 and 6-3 list the dosing guidelines for everolimus-related non-hematologic and hematologic toxicities. Table 6-4 provides guidelines for the management of everolimus-associated pneumonitis.

Table 6-2 Dosing guidelines for Everolimus-related non-hematologic toxicities

Toxicity	**Action**
Non-Infectious Pneumonitis	Please refer Table 6-4
Reactivation of HBV or HCV flare	Please refer to Section 6.2.1.7.
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. If resolution takes > 28 days, the patient comes off the study.
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 after dose reduction or toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus.
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia	Interrupt Everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.

Toxicity	**Action**
Any other grade 4 toxicity not listed here, including those involving the cardiac, endocrine, GI, metabolism, musculoskeletal, CNS, renal, respiratory, vascular, and cutaneous systems (CTCAE v4)	Hold Everolimus until recovery to grade ≤ 1 or baseline value Reintroduce Everolimus at one dose level lower, if available. If resolution takes > 28 days, the patient comes off the study.
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.
Recurrence of grade 4 after dose reduction	Discontinue Everolimus
Any non-hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus, take patient off study
* Should HCV flare be confirmed, the guidelines for flare must take precedence	

Table 6-3 Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	**Action**
Grade 2 thrombocytopenia (platelets <75, ≥ 50x10^9/L)	No action
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt Everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce Everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event recurs within 28 days, reintroduce Everolimus at one dose level lower, if available. If resolution takes > 28 days, the patient comes off the study.
Grade 4 thrombocytopenia (platelets < 25 x10^9/L)	Interrupt Everolimus until recovery to grade ≤ 1. Then reintroduce Everolimus at one dose level lower, if available. If resolution takes > 28 days, the patient comes off the study.
Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x10^9/L)	Interrupt Everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce Everolimus at the same dose level. If AE resolution occurs > 7 days, or event recurs within 28 days, reintroduce Everolimus at one dose level lower, if available. If resolution takes > 28 days, the patient comes off the study.
Grade 4 neutropenia or anemia	Interrupt Everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce Everolimus at one dose level lower, if available. * If resolution takes > 28 days, the patient comes off the study.
Febrile neutropenia	Interrupt Everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce Everolimus at one dose level lower, if available. * If resolution takes > 28 days, the patient comes off the study.
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available.
***Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction**	**Discontinue Everolimus**
***Any hematologic toxicity requiring Everolimus interruption for > 28 days**	**Discontinue Everolimus**

Table 6-4 Management of non-infectious pneumonitis

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

6.2.1 Management of specific toxicities

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2). Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in tables 6-2 and 6-3

6.2.1.1 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 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.

6.2.1.2 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.

6.2.1.3 Management of stomatitis / oral mucositis / mouth ulcers

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

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

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

6.2.1.4 **Management of diarrhea**

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with loperamide. Loperamide is taken 4 mg orally after the first loose stool, then 2 mg after each loose stool, not to exceed 16 mg in any 24-hour period.

6.2.1.5 **Management of hyperlipidemia and hyperglycemia**

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (>2.5x upper normal limit) should be treated with 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.

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

6.2.1.6 **Management of non-infectious pneumonitis**

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

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

Individuals participating in this trial will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. Moreover, potential lung radiological changes can be detected by the chest CT/MRI scans that are performed on all patients every 8 weeks for tumor assessment according to the schedule of events. In addition, pulmonary function tests (PFTs) will be conducted, if clinically indicated, to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in table 6-4 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

6.2.1.7 **Management of Hepatitis B and C Reactivation**

Patients with a history of hepatitis or significant exposure to hepatitis will be screened at the beginning of the study to assess activity of disease. Those with active hepatitis B or C are excluded from this protocol. Everolimus has been associated with reactivation of both hepatitis B virus (HBV) and hepatitis C virus (HCV). Patients entered on this study who subsequently show evidence of active hepatitis B or C will be withdrawn from the study.

6.3 Hepatic Impairment Dose Modifications

- Mild hepatic impairment (Child-Pugh A) – the recommended dose is 7.5 mg daily.

- Moderate hepatic impairment (Child-Pugh B) – the recommended dose is 2.5 mg daily (if deterioration in hepatic function is observed on study).
- Severe hepatic impairment (Child-Pugh C) – not recommended. If the desired benefit outweighs the risk, a dose of 2.5 mg daily must not be exceeded.
- Dose adjustments should be made if a patient's hepatic (Child-Pugh) status changes during treatment.

Everolimus is not recommended for patients with hepatic impairment who require doses below 2.5 mg every other day.

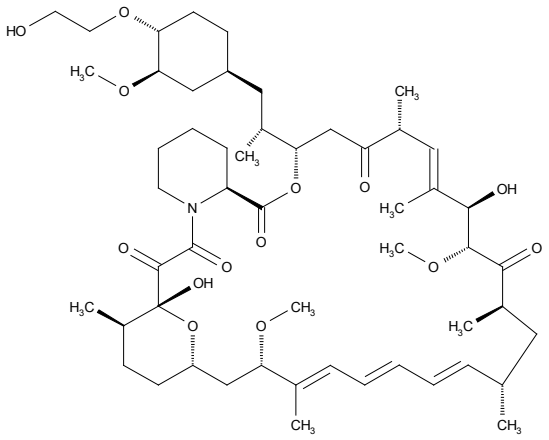
7. DRUG FORMULATION AND ADMINISTRATION

7.1 Everolimus

7.1.1 Description

Chemical Name and Structure

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



Pharmacokinetics

Absorption: Rapid, but moderate
Protein binding: ~74%
Metabolism: Extensively metabolized in the liver via CYP3A4; forms 6 weak metabolites
Bioavailability: Tablets: ~30%; systemic exposure reduced by 22% with a high-fat meal and by 32% with a light-fat meal

Half-life elimination: ~30 hours
Time to peak, plasma: 1-2 hours
Excretion: Feces (80%, based on solid organ transplant studies); Urine (~5%, based on solid organ transplant studies)
Drug Interactions: Substrate of CYP3A4 (major), P-glycoprotein

7.1.2 Form

Everolimus comes in 2.5 mg, 5 mg, and 10 mg tablets.

Tablets: It is recommended that Everolimus is taken in the morning, one hour prior to breakfast. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. For patients unable to swallow tablets, the tablet(s) should be dispersed completely in a glass of water (containing approximately 30 mL) by gently stirring, immediately prior to drinking. The glass should be rinsed with the same volume of water and the rinse completely swallowed to ensure the entire dose is administered. Everolimus missed doses may be taken up to 6 hours after regularly scheduled time; if > 6 hours, resume at next regularly scheduled time.

7.1.3 Storage and Stability

Everolimus should be stored at room temperature in a dry, dark location.

7.1.4 Compatibility

Not applicable

7.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment. Avoid contact with broken tablets.

7.1.6 Availability

Everolimus will be supplied free of charge by Novartis for this study.

7.1.7 Preparation

Everolimus will be made available in blister packs of tablets. No specific preparation will be required

7.1.8 Administration

Everolimus is taken orally once daily.

7.1.9 Ordering

Drug supply will be ordered by pharmacy personnel at each site using the Drug Request Form in Appendix B.

7.1.10 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

7.1.11 Destruction and Return

At the end of the study, unused supplies of everolimus should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetic Studies

As everolimus is an approved agent, no pharmacokinetic studies will be performed.

8.2 Pharmacodynamic Studies

8.2.1 Laboratory Correlative Studies

8.2.1.1 Whole exome sequence analysis of tumor specimen

Paraffin blocks of tumor biopsies or resection specimens will be collected at the time of study entry by the Principal Investigator for whole exome sequencing analysis. If paraffin blocks are not released by the pathology department, unstained slides maximum of 20 and minimum of 5 will be requested with each tissue cut measuring a minimum of 4 microns in width. These samples will be sent to the research laboratory of the Principal Investigator at the following address: David Kwiatkowski, Brigham and Women's Hospital, 20 Shattuck St., Thorn 826C, Boston, MA 02115. These samples will be used for DNA extraction and analysis by whole exome sequencing at the Broad Institute. A paired normal DNA sample is required

for this analysis and will be collected as a blood sample on the date of study entry. Whole exome data will be analyzed using standard pipeline tools in use at the Broad Institute, including Mutect to identify sequence variants present in the cancer and not in the normal DNA sample, and CapSeg to identify regions of significant copy number variation across the genome.

9. STUDY CALENDAR

Baseline evaluations are to be conducted within 1-week prior to start of protocol therapy. Scans must be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within **one week** of the protocol-specified date, unless otherwise noted.

Action	Study entry (within 14 days of day 1 unless otherwise noted))	Day1	At clinic visit every 4 weeks* (This may be extended to every 8 weeks after cycle 2 upon investigator's discretion)	Every 8 weeks for max. 24 months*	End of Study
Informed consent	**X (within 28 days of day1)**				
Medical history and height	**X**				
Inclusion/exclusion criteria	**X**				
Vital Signs	**X**	**X**	**X**		**X**
ECOG Performance status	**X**	**X**	**X**		**X**
Physical examination and weight	**X**	**X**	**X**		**X**
AE's and con-medications/treatments	**X**	**X**	**X**		**X**
Pregnancy test (female subjects <50)	**X (in clinic)**	**X**	**X (in clinic)**	**X****	
Hematology and blood chemistry	**X**	**X*****	**X**		**X**
Urinalysis	**X**	**X (only if abnormal at baseline or clinically indicated)**			
CT/MRI chest, abdomen, and other disease sites, as appropriate	**X (within 30 days of day 1)**			**Repeat scans of areas of known disease or of new areas based on clinical judgment**	
Everolimus		**Administered daily continuously until removal from study**			
Cf-DNA blood		**X**			
Archived tumor sample	**Sample must have been acquired no longer than 2 years prior to enrollment in the study**				
Tumor biopsy	**Participants who achieved either a partial response or stable disease ≥ 4 months must agree to a tumor biopsy upon disease progression, assuming it is judged safe and feasible by treating physician**				

- ***+/- one week depending on appointment availability due to holidays or unforeseen events**
- ****When women of child-bearing age are being seen every two months, it is recommended that they perform home pregnancy testing at 1 month between visits. They should also have an office pregnancy test at every visit. Patients will be contacted by a member of the study team via phone to track the pregnancy tests performed at home.**
- *****Hematology and blood chemistry studies need to be assessed on C1D1 only if screening was performed >72 hours prior. In this case laboratory values on cycle 1 day 1 must meet eligibility criteria.**

Hematology: hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

Chemistry: must include sodium, potassium, chloride, bicarbonate, calcium, glucose, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, uric acid, phosphorus, serum lipid profile (triglycerides, total cholesterol, HDL and LDL). *Because accurate serum glucose and lipid measurements are required, patients should be fasting at the time of the blood sampling.*

Urinalysis: Standard urinalysis dipstick assessment (pH, protein, glucose, blood, ketones, and leukocytes) should be performed at baseline. This must be supplemented with laboratory quantification of any potentially relevant abnormalities.

Physical Examination: General appearance, skin, head, neck, lungs, heart, abdomen, lymph nodes, extremities and basic nervous system.

cf-DNA blood: to be collected pre-dose on day 1 of cycle 1 using Cell- Free DNA BCT (Sterck) tube, 10ml or PAXgene, DNA tubes 8.5 ml . Store at room temperature (ambient) for same day shipment

10. MEASUREMENT OF EFFECT

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-

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 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al., 2009). Changes in the diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

10.1.1 Definitions

Evaluable for toxicity: All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response: Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.}

10.1.2 Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter >20 millimeters (mm) using conventional techniques (CT, MRI, x-ray) or >10 mm with spiral CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 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 $\geq$ 10 to < 15mm short axis, are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses identified by

physical exam that are not measurable by reproducible imaging techniques, and cystic lesions are all considered non-measurable.

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. Lesions must be accurately measured in 1 dimension with a minimum size of 10 mm by CT or MRI (slice thickness no greater than 5 mm), 20 mm by *chest* x-ray. Nodes must have a short axis ≥ 15 mm. The short axis should be included in the sum of the lesions in the calculation of response. Nodes that shrink to < 10 mm are considered normal. Target lesions should be selected on the basis of their size, be representative of all the involved organs, and should be lesions that can be followed with reproducible repeated measurements.

Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered target lesions if the *soft tissue component* meets the definition of measurability as defined above. Cystic lesions thought to represent cystic metastases can be considered as target lesions. However, if non-cystic lesions are present, these are preferred for selection as target lesions. Lesions in previously irradiated areas or areas subject to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression of that lesion.

Non-target lesions: All other lesions, including small lesions < 10 mm or pathological lymph nodes measuring ≥ 10 mm to < 15 mm in short axis, as well as truly non-measurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

10.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. 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 when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For 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 thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of 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.

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response (L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. Van den Abbeele, J. Yap, D. Sullivan. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med, 47(6):901-903, 2006). Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the

scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

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 subject to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

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.

10.1.4 Response Criteria

10.1.4.1 Evaluation of Target Lesions

Complete Response (CR):

Disappearance of all target lesions: Any pathological lymph node 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 with at least 5mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.

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.

Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing for target lesions, the overall assessment must be UN unless there is new disease that would result in an overall assessment of PD. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.2 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 subject to be considered in complete clinical response.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions* (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions. Overall level of substantial worsening that merits discontinuation of therapy. A useful test that can be applied when assessing non-targets for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

Unknown (UN): Assessment of non-target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

***Definition of New Lesion**: The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (ex: new bone lesions may be healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

10.1.4.3 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 participant'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 for 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	

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

Note: Participants 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	NonCR/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 an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

10.1.5 Duration of Response

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

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

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

10.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study registration to the date of documented disease progression or death, whichever occurs first. Patients not experiencing an event will be censored at the date of the last disease assessment.

11. ADVERSE EVENT REPORTING REQUIREMENTS

11.1 Definitions

11.1.1 Adverse Event (AE)

An adverse event (AE) is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

11.1.2 Serious adverse event (SAE)

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death

- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

11.1.3 Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

11.1.3.1 Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 6.1 for a listing of expected adverse events associated with the study agent(s).

11.1.3.2 Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

11.1.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

11.2 Procedures for AE and SAE Recording and Reporting

Participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

11.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the principal investigator, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3

with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.4 Reporting to the Study Sponsor

11.4.1 Serious Adverse Event Reporting

All serious adverse events that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the DF/HCC Overall Principal Investigator on the local institutional SAE form. This includes events meeting the criteria outlined in Section 11.1.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) Events – Only events that are unexpected and possibly, probably or definitely related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) Events – Unless expected AND specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) Events – When the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event to the DF/HCC Overall Principal Investigator within 1 business day of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

David Kwiatkowski, MD, PhD
Phone: (857) 307-0781

Fax: (617) 394-2762
dkwiatkowski@partners.org

Within the following 1-2 business days, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

11.4.2 Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the DF/HCC Overall Principal Investigator on the toxicity Case Report Forms.

11.5 Reporting to the Institutional Review Board (IRB)

Investigative sites within DF/HCC will report all serious adverse events directly to the DFCI Office for Human Research Studies (OHRS).

Other investigative sites will report SAEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional SAE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The Overall PI will submit SAE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

11.6 Reporting to Novartis Pharmaceuticals

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

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 by each participating study team within 1 business day of learning of its occurrence **(fax: 877-778-9739)**. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days. A copy of the report needs to be sent to the Protocol Sponsor at the fax number listed in section 11.4.1.

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 1 business day 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.

11.7 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any subject safety reports or sentinel events that require reporting according to institutional policy.

11.8 Monitoring of Adverse Events and Period of Observation

All adverse events, both serious and non-serious, and deaths that are encountered from initiation of study intervention, throughout the study, and within 30 days of the last study intervention should be followed to their resolution, or until the participating investigator assesses them as stable, or the participating investigator determines the event to be irreversible, or the participant is lost to follow-up. The presence and resolution of AEs and SAEs (with dates) should be documented on the appropriate case report form and recorded in the participant's medical record to facilitate source data verification.

For some SAEs, the study sponsor or designee may follow-up by telephone, fax, and/or monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. Participating investigators should notify the DF/HCC Overall Principal Investigator and their respective IRB of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12. DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with ODQ
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or

DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. For additional information, please refer to section 5 of the DSMP (Appendix C).

13. REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The DF/HCC Overall Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.3 Ethics and Study Execution

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
    - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
    - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
    - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
    - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- DF/HCC research policies and procedures http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-unit-cru/policies-and-procedures/

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI,

Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

14. STATISTICAL CONSIDERATIONS

This is a single-arm non-randomized phase II study evaluating the mTOR inhibitor everolimus in patients who have documented inactivating mutations in either TSC1 or TSC2, or activating mutations in MTOR. Preliminary data indicates that TSC1 and TSC2 mutations are present in approximately 5-10% of bladder cancer, 10% of pancreatic neuroendocrine tumors, 50% of PEComa, 2% of squamous cell lung cancer, and 5-10% of anaplastic thyroid cancer.

14.1 Study Design/Endpoints

The primary objective of this trial is objective response rate according to RECIST 1.1 criteria.

Secondary objectives include duration of response, progression-free and overall survival. Duration of response is defined as the time from RECIST-confirmed response (CR+PR) to documented disease progression. Progression-free survival is defined as the time from study registration to documented disease progression per RECIST 1.1 or death from any cause, whichever occurs first. Patients not experiencing a PFS event will be censored at the date of their last disease assessment. Overall survival is defined as time from registration to death from any cause, censoring patients thought to be alive at the time of final analysis at the last date of follow up. We will also estimate toxicity via CTCAE version 4.0, and the association of IHC and whole exome sequencing results with patient outcomes and other genetic events.

We will estimate event-time distributions using the Kaplan-Meier method, using Greenwood's formula to estimate the variance and provide 90% confidence intervals for the medians, 6-month, and 1-year estimates. Categorical outcomes, such as toxicity and response, will be estimated and their corresponding 90% exact binomial confidence intervals will be provided.

For the cohort of patients with TSC1 and TSC2 mutations, we will conduct this study using a Simon's two-stage design. In the first stage we will enroll 21 patients and if a total of at least 4 responses (CR + PR) are observed among them, accrual to the second stage will open. If 3 or fewer responses are observed among the first 21 patients, the study will terminate. In the second stage, an additional 29 patients will be enrolled for a total study accrual of 50 patients. After accrual to the second stage is completed, we will declare study success if at least 8 responses are observed among the 50 registered patients. This design has a probability of stopping early after the first stage of accrual of 85% if the drug is ineffective; the overall power of the study to detect the targeted response rate of 30% (compared to a null of 10%) is 91% while controlling the type I error at a one-sided level of 0.07.

For the cohort of 10 patients harboring mTOR mutations, we are somewhat limited in the inferences that can be made, however we would consider observing at least 2 responses in this cohort worthy of additional study. The maximum half-width of the 90% exact binomial confidence interval will be 23.5%.

14.2 Consideration of gene and mutation specific response rates

It is possible that certain combinations of mutation - primary cancer site will not respond to Everolimus therapy. Though the distribution of histologic subtypes among patients to be enrolled is unknown at this time, it is of interest to conduct exploratory analyses within these subgroups (for example, among patients with bladder cancer, PEComas, squamous cell lung cancer, etc.) Among a subgroup of 10 patients of any particular histology, there is 0.98 probability of observing at least 1 response among them, assuming an underlying response rate of 30%. Therefore, if 10 patients with TSC1/TSC2 mutations and a single cancer site are enrolled and no responses are observed among them, consideration may be given to halting enrollment of patients with cancers arising in that specific site. Since this lack of response may vary according to the primary site of cancer, in that instance we will continue to enroll patients TSC1/TSC2 mutations and different primary cancer sites.

14.3 Sample Size/Accrual Rate

We have a planned sample size of 30 patients, with either inactivating TSC1 or TSC2 mutations, or activating MTOR mutations, so it is estimated that this protocol will complete accrual in 48 months, making for an overall accrual rate of approximately 1.25 patients per month. We will be identifying patients for this study from the Oncopanel cancer genotyping at DFCI/BWH, the Impact cancer genotyping panel at MSKCC, and CLIA certified genotyping laboratories both at other DF/HCC institutions and external sites.

15. PUBLICATION PLAN

The results will be made public within 12 months of the end of the last patient's last visit. The initial release of data will be in a peer-reviewed journal or in an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of outcomes will be made public no later than three years after the end of data collection.

16. REFERENCES

1. Boulay A, Lane HA. The mammalian target of rapamycin kinase and tumor growth inhibition. Recent Results Cancer Res. 2007;172:99-124.
2. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med. 2005;353:2477-90.
3. Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. Nat Rev Cancer. 2004;4:335-48.
4. Frattini M, Signoroni S, Pilotti S, Bertario L, Benvenuti S, Zanon C, et al. Phosphatase protein homologue to tensin expression and phosphatidylinositol-3 phosphate kinase mutations in colorectal cancer. Cancer Res. 2005;65:11227.
5. Velho S, Oliveira C, Ferreira A, Ferreira AC, Suriano G, Schwartz S, et al. The prevalence of PIK3CA mutations in gastric and colon cancer. Eur J Cancer. 2005;41:1649-54.
6. Goel A, Arnold CN, Niedzwiecki D, Carethers JM, Dowell JM, Wasserman L, et al. Frequent inactivation of PTEN by promoter hypermethylation in microsatellite instability-high sporadic colorectal cancers. Cancer Res. 2004;64:3014-21.
7. Bissler JJ, Kingswood JC, Radzikowska E, Zonnenberg BA, Frost M, Belousova E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2013.
8. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2013;381:125-32.
9. Dickson MA, Schwartz GK, Antonescu CR, Kwiatkowski DJ, Malinowska IA. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. Int J Cancer. 2013;132:1711-7.
10. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, Qin W, Fletcher CD, Vena N, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. J Clin Oncol. 2010;28:835-40.
11. Iyer G, Hanrahan AJ, Milowsky MI, Al-Ahmadie H, Scott SN, Janakiraman M, Pirun M, Sander C, Socci ND, Ostrovnaya I, Viale A, Heguy A, Peng L, Chan TA, Bochner B, Bajorin DF, Berger MF, Taylor BS, Solit DB. Genome sequencing identifies a basis for everolimus sensitivity. Science. 2012 338:221.
12. Voss MH, Hakimi AA, R. BA, Scott S, Takeda S, Liu HL, Chen Y, Motzer RJ, Berger MF, Hsieh JT. Next-generation sequencing reveals genomic determinants of long-term response to mTOR inhibitors in patients with advanced RCC. BJUI 2013 11th International Kidney Cancer Symposium Annual Meeting.
13. Wagle N, Grabiner BC, Van Allen EM, Hodis E, Jacobus S, Supko JG, Stewart M, Choueiri TK, Gandhi L, Cleary JM, Elfiky AA, Taplin ME, Stack EC, Signoretti S, Loda M, Shapiro GI,

Sabatini DM, Lander ES, Gabriel SB, Kantoff PW, Garraway LA, Rosenberg JE. Activating mTOR mutations in a patient with an extraordinary response on a phase I trial of everolimus and pazopanib. Cancer Discov. 2014 4:546-53.
14. Grabiner BC, Nardi V, Birsoy K, Possemato R, Shen K, Sinha S, Jordan A, Beck AH, Sabatini DM. A diverse array of cancer-associated MTOR mutations are hyperactivating and can predict rapamycin sensitivity. Cancer Discov. 2014 4:554-63.

17. APPENDICES

Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B: Drug Order Form

RAD001
DRUG REQUEST FORM
Investigational Supply

Please e-mail request to: maritza.crawford@novartis.com

Date:

Study Title: **A Phase II trial of everolimus for cancer patients with inactivating mutations in TSC1 or TSC2**

Investigator's Name: **David J. Kwiatkowski, MD, PhD**

Novartis Protocol Number: **CRAD001 MUS217T**

Requestor's Name:

Requestor's Phone#:

Institution: **Dana-Farber/Harvard Cancer Center**

Shipping Address: **David J. Kwiatkowski, MD, PhD**
Attn: Beth Meyers
450 Brookline Avenue, Yawkey 5
Boston, MA 02215

Shipping Phone#: **617-632-4254**

Is this Initial Shipment:
Yes **No**

Date by when this shipment is required^:

18. Drug	Label Strength	Quantity in boxes*

RAD001	**10 mg**	
RAD001	**5mg**	
RAD001	**2.5 mg**	

^Please allow 10-14 days for processing of this request and delivery of the shipment.

*** Tablets are supplied in blister cards in kits/boxes of 28 tabs**

If you encounter problems, please email: maritza.crawford@novartis.com

RAD001
DRUG REQUEST FORM
Investigational Supply

Please e-mail request to: maritza.crawford@novartis.com

Date:

Study Title: **A Phase II trial of everolimus for cancer patients with inactivating mutations in TSC1 or TSC2**

Investigator's Name: **David J. Kwiatkowski, MD, PhD**

Novartis Protocol Number: **CRAD001 MUS217T**

Requestor's Name:

Requestor's Phone#:

Institution: **MSKCC - Pharmacy**

Shipping Address: **Gopakumar Viyer**
ATTN: Gerald O'Neill

1275 York Ave, C-1087
New York, NY 10065

Shipping Phone#: _____

Is this Initial Shipment:
Yes No

Date by when this shipment is required^: _____

19. Drug	Label Strength	Quantity in boxes*
RAD001	**10 mg**	
RAD001	**5mg**	
RAD001	**2.5 mg**	

^Please allow 10-14 days for processing of this request and delivery of the shipment.

*** tablets are supplied in blister cards in kits/boxes of 28 tabs**

If you encounter problems, please contact maritza.crawford@novartis.com

Appendix C: Data and Safety Monitoring Plan

DFCI IRB Protocol #: 14-229

APPENDIX C

Dana-Farber/Harvard Cancer Center

Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (Food and Drug Administration (FDA), etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.
Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC

Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol. Should the DF/HCC Sponsor decide to use a CRO, the CRO will be deemed the Coordinating Center.

DF/HCC Quality Assurance Office for Clinical Trials: A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, David Kwiatkowski, MD, Ph.D. will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCCODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal Wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.2.1 Coordinating Center Contact Information

The DF/HCC Coordinating Center will consist of designees from the Early Drug Development Center (Phase I). Responsibilities are specified below, although may be updated based on the DF/HCC Sponsor discretion.

Central email address to be used for general site questions and regulatory functions: dfcieddc_regulatory@dfci.harvard.edu

Teleconferences, INDSR and SAE review and circulation, overall coordination of accrual, etc.: Ketki Bhushan (Study Coordinator)
Phone: (617) 632-4270
Email: kbhushan@partners.org

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC requirements. Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the

Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
- Participating Institution’s IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Eligible participants will be registered onto the trial with the DF/HCC Office of Data Quality (ODQ) central registration system. Registration must occur prior to the initiation of therapy. Registration should occur during ODQ's normal business hours, Monday through Friday from 8:00AM to 5:00PM Eastern Time. Same day treatment registrations and off-hour registrations for a participant at a non-DF/HCC site will only be accepted with prior notice and discussion with the Coordinating Center.

3.7.2 Participant Registration at a non-DF/HCC Site

Eligible participants will be entered on study centrally at the Coordinating Center by the Study Coordinator. All sites should call the Study Coordinator to verify dose level availabilities. The required forms mentioned below will be provided to sites by the Coordinating Center during site activation. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be cancelled. The Study Coordinator should be notified of cancellations as soon as possible.

To register a participant at any non-DF/HCC site, the subsequent procedures must be followed. Contact information for the Coordinating Center is located in section 2.2.1:

1. The Participating Site should contact the Coordinating Center to:
    a. Notify regarding a potential participant
    b. Confirm the methods of sending documents and communication for the registration
    c. Communicate desired timeline for the registration and start date

2. The Participating Site should send the following documents to the Coordinating Center:
    a. Completed DF/HCC Eligibility Source Worksheet (ESW), which will be provided to site
    b. Copy of all protocol required screening test results, as requested on the ESW
    c. Copy of the pathology and surgical reports, as requested on the ESW
    d. List of all concomitant medications with review by a clinician
    e. Copy of the signed informed consent document
    f. Copy of the signed HIPAA authorization form (if separate from the informed consent document)

3. After having received all documentation, the Coordinating Center will review the documents to verify eligibility.

4. The Coordinating Center will register the participant with ODQ and subsequently inform the participating site of the successful registration via fax or email which will include:
    a. Participant Identification Number
    b. Applicable dose treatment level

5. **Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.**

6. After the participant is registered, additional documentation is to be sent to the Coordinating Center if it was not provided in the initial submission. The specifics and timeline of this will be specified by the Coordinating Center within the instructions of the Eligibility Source Worksheet.

NOTE: Registration and randomization with ODQ can only be conducted during the business hours of 8:00AM and 5:00PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

3.7.3 Participant Registration at a DF/HCC Site

Please refer to section 4.2 of the protocol

3.7.4 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.5 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, ODQ requires the following identifiers for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.9 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

3.9.2 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC

Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.10 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.10.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.10.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.11 Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

3.11.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 7.
Participating Institutions should order their own agent regardless of the supplier. (i.e., a pharmaceutical company).

For investigational agents (Everolimus), participating institutions should ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Additionally, sites will be required to participate in Coordinating Center initiated teleconferences.
These will be planned for bi-weekly during Stage 1 of the protocol and monthly during Stage 2, although they may be more/less frequent at the discretion of the Protocol Chair. During the teleconferences, sites will be expected to convey the following information:

- Updates on participants taking agent: holds, dose reductions, significant events, how the participant is doing, whether or not underwent re-consenting
- Protocol status – which version is being used, and the status of any amendments
- Any reportable adverse events or deviations/violations that have yet to be submitted
- Review of prospective patients

If sites are not able to have a representative participant present at the teleconferences, they should email this information to the Coordinating Center.

Virtual Monitoring will be the primary mode of monitoring, although on-site monitoring may occur if felt to be necessary by the Coordinating Center and Protocol Chair. Upon request, sites will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification.

Virtual monitoring of participant eligibility, human subject's protection via the initial informed consent document and process, and screening evaluation completion will occur, if feasible, within 2 weeks of the first participant registration.

Interim monitoring visits will occur on the following schedule:
Once a site has registered a participant, up until all participants have discontinued taking study agent (may be in follow-up), interim monitoring visits will occur approximately every 6 months, with the primary mode being virtual visits. This frequency may be adjusted depending on accrual, site compliance and Protocol Chair discretion. The first

interim monitoring visit will occur approximately two months after the registration of the site's first participant.

Once a site is closed to accrual and all participants have discontinued study agent, interim monitoring visits will occur approximately annually until study completion.

Monitoring visits will focus on reviewing some or all of the following:

- Adverse events and altered results
- Response assessment including measurements and clinical assessments
- Study drug administration and accountability
- Concomitant medications
- Consent and re-consenting
- Presence of key documents: original consent, eligibility and screening source information, registration confirmation, off treatment and off study forms, collection and transfer of samples
- Reason off treatment and reason off study
- Timeliness of data completion
- Completion of study procedures per protocol
- Agreement between recorded results and source documentation
- Analysis of data for any events that meet criteria for reportable adverse events, dose holds, dose reductions, or discontinuation of treatment
- Regulatory binder: accessibility, organization, random sampling for relevant documents and agreement with the trial master file
- Collection of research samples per protocol and appropriately entered onto CRFs, as this will be the primary mode of tracking samples across sites

The Coordinating Center will be available to all sites' study team members for resolving questions and concerns and facilitating compliance.

All data submitted to the DF/HCC ODQ will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. The Coordinating Center and if applicable, ODQ Data Analysts assigned to the protocol, will perform the ongoing protocol data compliance monitoring.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. The minimum accrual requirements for this study are 10 subjects per site per year. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: DF/HCC Sponsored Trials

This study is IND exempt and a combination of virtual and on-site monitoring will be performed by an experienced DF/HCC monitor (Clinical Research Specialist). According to the DF/HCC MCC audit plan guidelines a formal Audit plan is not required for this trial. An audit may be performed by the ODQ at the request of the DF/HCC Sponsor if instances on non-compliance are found during routine monitoring.

6.2 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.