FOX CHASE CANCER CENTER
TEMPLE HEALTH

A Phase II study of Sporadic Angiomyolipomas (AMLs) Growth Kinetics while on Everolimus Therapy (SAGE)

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Sponsor Investigator:
Robert Uzzo, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Department of Surgical Oncology
Philadelphia PA 19111
Phone: 215-728-3096
Email: robert.uzzo@fccc.edu

Co-Investigators:
Daniel M. Geynisman, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Department of Medical Oncology
Philadelphia, PA 19111
Phone 215-728-3889
Email: daniel.geynisman@fccc.edu

Barton Milestone, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Department of Medical Oncology
Philadelphia, PA 19111
Phone 215-728-3024
Email: Barton.Milestone@fccc.edu

Radiologists:

Rosaleen Parsons, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Department of Medical Oncology
Philadelphia, PA 19111
Phone 215-728-3024
Email: rosaleen.parsons@fccc.edu

Barton Milestone, M.D.
Fox Chase Cancer Center
333 Cottman Avenue
Department of Medical Oncology
Philadelphia, PA 19111
Phone 215-728-3024
Email: Barton.Milestone@fccc.edu

Statistician:

Eric Ross, PhD
Fox Chase Cancer Center
333 Cottman Avenue
Biostatistics/Bioinformatics and Population Studies Facilities
Philadelphia PA 19111
Phone: 215-728-2891
Email: eric.ross@fccc.edu

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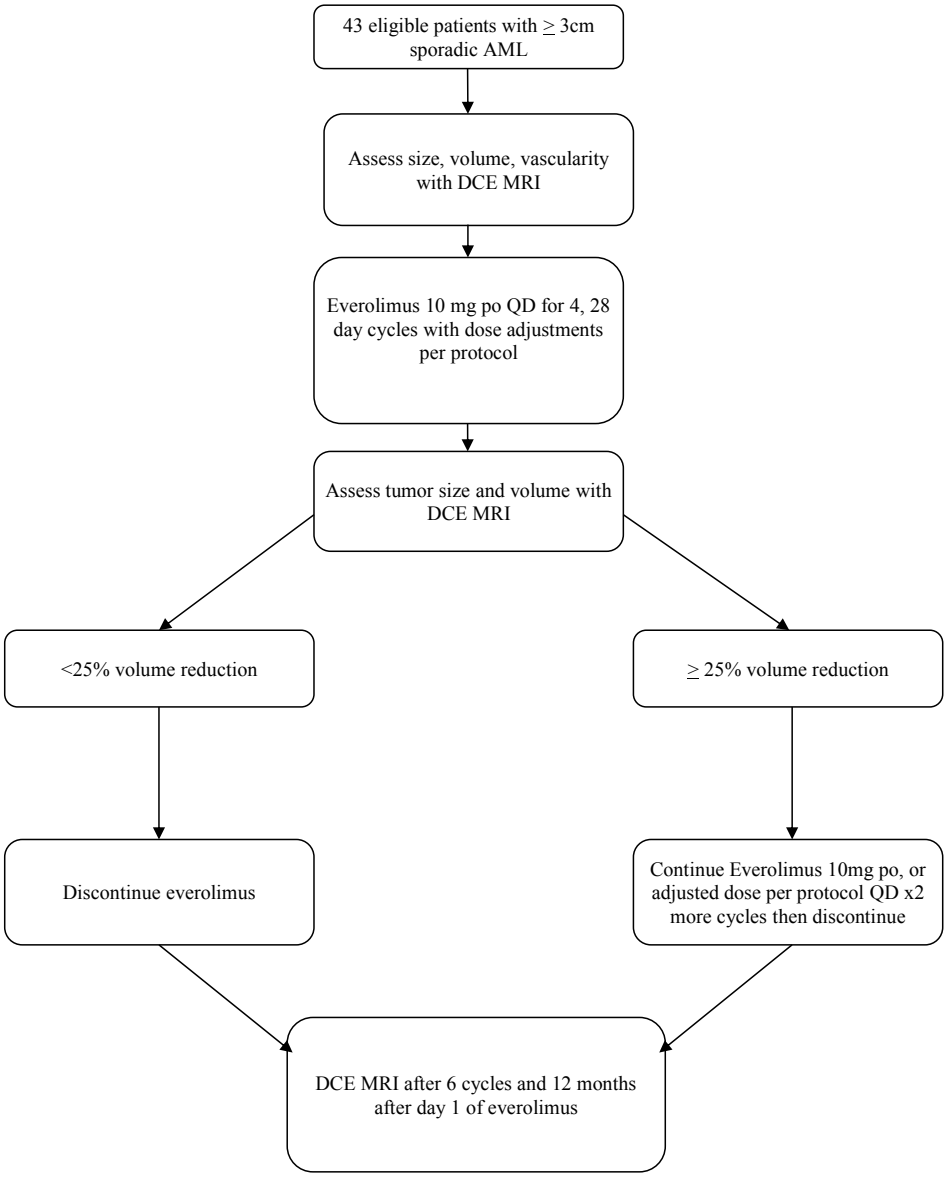
Study Schema



1.0 Introduction

1.1. Background

Renal angiomyolipomas (AMLs) are the most common benign tumors of the kidney[1]. They are composed of varying proportions of aneurysmal vascular cells, immature smooth muscle cells and fat cells. Clinically, the most worrisome aspect of AMLs is their propensity to rupture or spontaneously and bleed causing pain and occasionally acute life-threatening hemorrhage with up to 20% of patients presenting to the emergency room already in shock due to retroperitoneal bleeding[1]. The risk of this appears to be directly proportionate to the size of the lesion. This has led to the current clinical standard of care of surgical or percutaneous intervention (embolization) for patients with asymptomatic sporadic AMLs > 3-4 cm[1]. These interventions are not without risk and can lead to renal loss in the affected kidney with the long-term risk of chronic kidney disease/end-stage renal disease.

While sporadic AMLs are common, particularly in middle aged women, bilateral multifocal AMLs are strongly associated with tuberous sclerosis and exhibit constitutive activation of mammalian target of rapamycin (mTOR)[2].

In this population, a recent double blinded, placebo controlled phase III trial (EXIST-2) was performed in patients aged 18 years or older with at least one AML 3 cm or larger in its longest diameter. Patients were randomly assigned, in a 2:1 fashion to receive everolimus 10 mg per day or placebo. The primary efficacy endpoint was the proportion of patients with confirmed response of at least a 50% reduction in total volume of target angiomyolipomas relative to baseline. In the most updated analysis presented by Bissler at the 2014 World TSC Conference (unpublished), the authors noted an AML response rate of 53.6% for everolimus and 0% for placebo with an acceptable safety profile demonstrating a non-surgical treatment for AMLs associated with tuberous sclerosis[2]. On the basis of this trial, mTOR inhibitors have been felt to be effective in reducing the size of AMLs in patients with tuberous sclerosis complex (TSC) leading to a recent FDA approval for everolimus for AMLs in this population.

While there have been some case reports using mTOR inhibitors for advanced AMLs[34], there have been no prospective trials assessing outcomes and growth inhibition in sporadic AMLs in non-tuberous sclerosis populations. Here we propose to investigate the use of everolimus in a population of patients with sporadic AMLs who would otherwise be advised to undergo surgical or percutaneous intervention.

1.2. Agent under Investigation

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. 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[5].

Everolimus is being investigated as an antitumoral 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).

1.3. mTOR pathway and cancer

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

The main known functions of mTOR include the following[6]:

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers[7]
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers[8]
- 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

1.4. Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines in vitro including cell lines originating from lung, breast, prostate, colon, melanoma, and glioblastoma. IC50s range from sub/low nM to µM. Everolimus also inhibits the

proliferation of human umbilical vein endothelial cells (HUVECS) in vitro, with particular potency against VEGF-induced proliferation suggesting that everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of everolimus was confirmed in vivo. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls.

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

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

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

In vivo studies investigating the anti-tumor activity of everolimus in experimental animal tumor models showed that everolimus monotherapy typically reduced tumor cell growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

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

All significant adverse events observed in toxicology studies with everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or

4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

1.5. **Study Rationale**

In a randomized trial evaluating 118 patients from 24 centers with a known history of TSC or sporadic lymphangioleiomyomatosis (LAM) (EXIST-2), patients were randomized 2:1 to receive everolimus (n=79) or placebo (n=39). The AML response rate was 42% for the everolimus group and 0% for placebo with response rate defined as a radiographically confirmed reduction of at least 50% target volume. Moreover, everolimus was well tolerated with only two patients discontinuing medication due to adverse events[9,10]. Due to the clear superiority of everolimus, patients initially randomized to placebo were offered everolimus and in total 112 participants received everolimus. At the most updated analysis presented in July 2014 by Bissler (unpublished), the renal AML response rate was 53.6% with progression free rate of 89.4% at 36 months. Nine patients (8%) discontinued the study due to adverse events.

In regard to toxicity from everolimus, there is now a well-defined experience with this drug in multiple clinical settings, as reflected by the FDA drug label. More specifically, in those patients with TSC undergoing treatment with everolimus the most frequent adverse drug reactions have been stomatitis, amenorrhea, upper respiratory tract infections, hypercholesterolemia, nasopharyngitis, acne, menstruation irregular, sinusitis, and pneumonia. The most frequent grade 3/4 adverse reactions were stomatitis, amenorrhea, pneumonia, neutropenia, pyrexia, and gastroenteritis viral. In the updated EXIST-2 data, grade 3 AEs were noted in 3.6% for decreased blood phosphorus, 2.7% for amenorrhea; grade 4 AEs were noted in 1.8% for increased blood uric acid and 1% for convulsion, hydrocephalus, hypertensive crisis, neutropenia, pancreatic carcinoma and rhabbdomyolysis[2].

These data provoke inquiry into the far more common clinical scenario of patients with sporadic AMLs[11121314]. Although comparatively robust literature does not exist for sporadic AMLs, preclinical data seems to indicate that aberrant mTOR signaling is equally prevalent in sporadic AMLs[15]. Kenerson et al examined the activity of this pathway in sporadic AMLs and PEComas using immunohistochemical and biochemical analyses and report increased levels of phospho-p70S6K, a marker of mTOR activity, in 15 of 15 sporadic AMLs **15**. This finding was accompanied by reduced phospho-AKT expression suggesting disruption of TSC1/2 function. In their study Western blot analysis confirmed mTOR activation concurrent with the loss of TSC2 and not TSC1 in sporadic AMLs. Similarly, elevated phospho-p70S6K and reduced phospho-AKT expression was detected in 14 of 15 cases. Taken together, these observations provide functional evidence that mTOR activation is common to sporadic, non-TSC-related AMLs and suggest the possibility that mTOR inhibitors such as everolimus may be therapeutic for non-hereditary AMLs.

Here we hypothesize that inhibition of the mTOR pathway may be an effective therapeutic strategy in patients with sporadic AMLs. While EXIST-2 data demonstrate mTOR inhibition is unlikely to induce a complete response with disappearance of the

lesions, they do suggest a role for mTOR inhibitors in "resetting the biological clock" by decreasing tumor volume and thereby decreasing or delaying the risks/need for intervention. The strategy of resetting the "biological clock" has evolved from the collective experience with surgically managing renal tumors in patients with Von Hippel-Lindau (VHL) where this strategy is now considered the standard of care in the absence of curative interventions[16]. In the context of AMLs, resetting the biological clock suggests the ability to reduce the size of the tumor to <3cm and potentially reset future growth rates to delay or avoid the need for intervention.

Given the above considerations, herein we seek to study the role of everolimus in (1) reducing the size/volume of clinically significant sporadic AMLs (>3cm) (2) quantitating re-growth upon discontinuation of the agent and (3) minimizing symptoms and the need for intervention within 12 months following discontinuation.

2.0 Objectives

2.1. Primary Objective

1) To evaluate the efficacy and tolerability of everolimus in reducing tumor volume in sporadic AMLs as measured by dynamic contrast enhanced MRI (DCE MRI), in patients who might otherwise be considered for active surgical or percutaneous intervention.

2.2. Secondary Objectives

1) To evaluate health-related quality of life (HRQoL) in subjects treated with everolimus for sporadic AMLs.
2) To assess the growth kinetics of sporadic AMLs in patients who have been treated with everolimus.
3) To measure the rate of surgical or percutaneous (embolization) intervention at 1 year from day 1 of study.
4) To assess the safety of everolimus in patients with sporadic AML.

2.3. Exploratory Objectives

1) To determine whether volumetric response rates in sporadic AMLs to everolimus qualitatively correspond to perfusion/angiogenic content/vascularity of baseline tumor as measured by qualitative DCE MRI using the principles of Choi response criteria (AUC for first 30 seconds post injection).
2) To investigate and explore potential molecular mechanism(s) of response and/or resistance of sporadic AMLs to everolimus treatment using a) initial diagnostic tumor tissue samples and if a biopsy or tumor resection is clinically indicated and pursued that tumor tissue sample and b) serum cfDNA.

3.0 Study Plan

After confirming eligibility criteria, patients will be enrolled in this study. Volumetric and perfusion/vascularity analyses will be done by DCE-MRI at baseline. Patients will then receive everolimus 10 mg daily. Treatment duration will be continuous for 4 cycles unless treatment is discontinued.

After 4 cycles of treatment, repeat imaging with DCE-MRI will be performed to assess tumor size kinetics (sum of volumes of all target AMLs identified at baseline). If the tumor has decreased in size by greater than or equal to 25% and no new AMLs greater than 1 cm in longest diameter have appeared, then the drug will be continued for another two cycles (6 cycles total treatment). If on the other hand the tumor has grown or decreased by less than 25% or there are new AMLs (at least 1 cm in longest diameter), then the drug will be discontinued.

At the end of cycle 6 and 12 months after start of therapy with everolimus, imaging via DCE MRI will be repeated to assess growth/regrowth kinetics/qualitative perfusion.

If for any reason a patient terminates treatment with everolimus earlier than the end of cycle 4, all imaging will still be performed and used for the statistical analysis and primary endpoint calculations. Given that therapy with everolimus has potential toxicity and that the disease in question (sporadic AML) is not a malignant condition, patients will not be replaced if they drop out, in a way signaling that the therapy may not be feasible. If a patient receives at least one dose of everolimus they will be included in the analysis. If a patient does not get imaged after 4 cycles of treatment, for the purposes of statistical considerations they will be considered a non-responder.

Treatment related toxicities and QOL will be assessed at baseline, day 1 of each 28 day cycle, at drug discontinuation and at the last study visit

Tissue for exploratory objectives will be collected at baseline only if available from archival tissue. Additional tissue will also be collected if the patient undergoes a partial or complete nephrectomy or embolization during the study period for the AML. Serum at baseline will also be collected for cfDNA and other future potential correlative studies.

4.0 Patient Selection

4.1. Inclusion Criteria

4.1.1 18 years of age or older

4.1.2 A diagnosis of renal AML > 3 cm confirmed on pre-enrollment DCE MRI. A previous diagnosis or treatment of a different AML lesion is allowed.

4.1.3 ECOG Performance Status 0 or 1

4.1.4 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count > 1,500/mcL

- Hemoglobin ≥ 10 g/dL
- Platelets > 100,000/mcL
- AST/ALT (SGOT/SGPT) < 2.5 X ULN
- Total bilirubin ≤ 2.0mg/dL
- Renal Function eGFR > 30 mL/min via calculated creatinine clearance
- Fasting serum cholesterol ≤ 300 mg/dL **OR** ≤ 7.75 mmol/L
- Fasting triglycerides ≤300 mg/dL or ≤1.71 mmol/L.

4.1.5 Ability to understand and willingness to sign a written informed consent and HIPAA consent document

4.2. **Exclusion Criteria**

4.2.1 History of tuberous sclerosis, LAM or any active malignancy

4.2.2 Active treatment with any other investigational agents

4.2.3 Administration of any investigational drug within 30 days or 5 half-lives, whichever is longer, preceding the first dose of study treatment.

4.2.4 Concurrent therapy given to treat cancer

4.2.5 Patients must not have received any prior treatment for AML

4.2.6 Diagnosis of any other malignancy within 3 years prior to registration, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix or melanoma in-situ or low grade (Gleason 6 or below) prostate cancer on surveillance with no plans for treatment intervention (eg, surgery, radiation or castration).

4.2.7 Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

- Active peptic ulcer disease
- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation.
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment

4.2.8 Active diarrhea of any grade.

4.2.9 Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:

- Malabsorption syndrome
- Major resection of the stomach or small bowel resulting in dumping syndrome or clinical signs of malabsorption

4.2.10 Active or prior history of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (screening for all three is mandatory prior to study)

4.2.11 Presence of any active or ongoing infection.

4.2.12 Any known uncontrolled underlying pulmonary disease by history, physical exam or if applicable PFTs (e.g. FEV1 or DLCO 50% or less of predicted OR O2 saturation 88% or less at rest on room air).

4.2.13 History of any one or more of the following cardiovascular conditions within the past 6 months:

- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Coronary artery bypass graft surgery
- Symptomatic peripheral arterial vascular disease

4.2.14 History of Class III or IV congestive heart failure, as defined by the New York Heart Association Classification of Congestive Heart Failure. See Appendix I for NYHA Classification Table.

4.2.15 History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
Note: Patients with recent DVT who have been treated with therapeutic anticoagulation agents for at least 6 weeks are eligible as long as their INR is stable and within inclusion criteria per 4.1.4

4.2.16 Corrected QT interval (QTc) > 480 milliseconds as corrected by the Fridericia formula

4.2.17 Poorly controlled hypertension, defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg.
Note: Screening/Baseline blood pressure (BP) must be assessed with three measurements at approximately 2-minute intervals. The mean SBP / DBP values from the three readings must be <140/90 mmHg in order for a subject to be eligible for the study. If the subject's initial screening SBP/DBP is ≥ 140/90 mmHg, initiation or adjustment of antihypertensive medication(s) is permitted in an attempt to control the subject's BP level to below 140/90 mmHg. Optimal blood pressure control must be achieved before registration and monitored.

4.2.18 Evidence of active bleeding or bleeding diathesis

4.2.19 Patients must not have uncontrolled diabetes mellitus (defined by a Hgb A1c >8) obtained within 14 days prior to registration. Optimal glucose control (Hgb A1c ≤ 8) must be achieved before registration and monitored during protocol treatment

4.2.20 Unable or unwilling to discontinue use of prohibited medications within 14 days prior to randomization and while on treatment:

- No chronic treatment with systemic steroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- Growth factors (e.g. G-CSF, G-GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.
- Live vaccines must not be administered to patient due to immunosuppressant potential of everolimus.
- Drugs known to be strong inhibitors or inducers of CYP3A4 must not be administered. Drugs or substances known to be moderate inhibitors or inducers of CYP3A should be avoided if possible or used subject to caution as these can alter everolimus metabolism. Co-administration with strong or moderate inhibitors of P-glycoprotein (PgP) should be avoided if possible, or used subject to caution Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.

4.2.21 Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to everolimus that in the opinion of the investigator contraindicates their participation.

4.2.22 Prior or current use of systemic anti-VEGF inhibitors, cytokines or mTOR inhibitors (e.g. interferon, interleukin 2).

4.2.23 Patients with Child-Pugh A-C liver disease (See Appendix II: Child-Pugh Criteria)

4.2.24 Pregnant or nursing (lactating) women

4.2.25 Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 8 weeks after stopping treatment. Highly effective contraception methods include total abstinence, male partner sterilization (with post-vasectomy documentation of the absence of sperm in the ejaculate), or a combination of **any two** of the following:

- Use of oral, injected or implanted hormonal methods of contraception
    - In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

Women are considered to be physiologically capable of becoming pregnant unless:

- They have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms);
- They have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization.
    - In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

4.2.26 Male patients whose sexual partner(s) are WOCBP must agree to use adequate contraception as defined above during the study and for 8 weeks after the end of treatment. Condom use is required by all male patients in order to prevent delivery of the drug via seminal fluid.

4.2.27 Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures. Patients with low risk prostate and bladder cancer will be excluded (use AUA guidelines for bladder patients).

4.3. Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4. Participant Registration

Participants may be registered from 8:00 am to 4:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email **FCCC.MONITOR@fccc.edu** or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 Treatment Plan

Patients will be treated with Everolimus for 4, 28 day cycles. At the end of the fourth cycle, patients who have experienced a partial response (PR) defined as a reduction of 25% or more will continue therapy for an additional 2 cycles.

Patients with be treated continuously barring toxicity related delays. Missed days will not be made up. Patients will document adherence in a pill diary and should be directed to contact their treating physician with the onset of any side effects for further direction.

5.1. Treatment Administration Tables

Treatment Administration				
Agent	**Dose**	**Route**	**Schedule**	**Length**
Everolimus	10 mg	Oral	Daily	4 Cycles

If ≥ 25% volume reduction and no new AMLs are seen after 4 Cycles, continue as follows:				
Everolimus	10 mg	Oral	Daily	2 Cycles

5.2. Duration of Therapy

Patients will receive no more than 6 cycles of therapy in total.

5.3. Duration of Follow up

Patients will be followed for 1 year from the initiation of treatment for radiographic evaluation of their AML(s). Thus, maximum time on trial is 12 months. Patients who stop receiving Everolimus due to unacceptable adverse events will still be followed until the end of the study.

5.4. Criteria for Discontinuation

Patients will be removed from treatment if one of the following criteria applies:

- Disease progression including:
  - Bleeding or pain
  - Requirement for surgical or percutaneous intervention
  - Greater than a 25% increase in tumor volume of AML
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse events
- Treatment is temporarily held for > 21 days
- Patient becomes pregnant
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

The reason for discontinuation and the date the patient was removed must be documented in the medical record and case report form.

5.5. Optional Tissue and Blood Collection for Exploratory Objectives

At time of trial initiation, patients will be consented to allow the use of their tissue and blood for future research, specifically including, but not limited to, the analysis of mTOR alterations, VEFG pathways and tumor genome sequencing (e.g. mutations (AKT/PI3K, PTEN), amplifications, deletions in TSC1 and TSC2).

At screening, if archival biopsy tissue of the AML is available, unstained slides will be requested. If a patient undergoes a clinical procedure where tissue will be obtained during the study, that tissue will also be collected for exploratory objectives. Biopsy, resection, and/or percutaneous intervention will be performed entirely at the discretion of the treating clinician based on individual clinical scenarios and needs.

An EDTA and red top tube will be collected to provide plasma, serum and peripheral blood mononuclear cells (PBMCs). All biological samples will be stored at Fox Chase Cancer Center for possible future research.

6.0 Dosing, Toxicity and Specific Adverse Events

6.1. Dosing regimen

Everolimus should be taken orally once daily at the same time every day, either consistently with or consistently without food

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. 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.
If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead to immediately contact the study center as soon as possible to ask for advice.

6.2. Description of selected adverse drug reactions

In clinical trials and post-marketing spontaneous reports, everolimus has been associated with serious cases of the following:

- Hepatitis B reactivation, including fatal outcome.
- Reactivation of infections is an expected event during periods of immunosuppression.
- Renal failure events (including fatal ones) and proteinuria. Monitoring of renal function is recommended.
- Amenorrhea (including secondary amenorrhea).
- Pneumocystis jirovecii pneumonia (PJP) some with a fatal outcome.
- Angioedema has been reported with and without concomitant use of everolimus and ACE inhibitors

6.3. 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. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction. Once dose is reduced, patients will continue at new dose. No dose re-escalations are allowed. Details of study treatment schedule adjustments for Everolimus-related toxicities and dose levels are provided in the below tables.

6.3.1. Dose adjustments and dose levels:

Dose level	Dose and schedule
0 (starting dose)	10mg
1	5mg
2	5mg 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.

6.3.2. Non-hematologic toxicities

Toxicity	**Action**
Non-Infectious Pneumonitis	Please refer to **6.3.4**.
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 or higher (> 5.0 ULN)*	• Discontinue study drug permanently
Intolerable grade 2 mucositis,	• 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 21 days.
Recurrence of intolerable grade 2 mucositis	• Reduce dose to the next lower dose level, if available.
Grade 2 hyperlipidemia or hypertriglyceridemia	• Reduce dose to the next lower dose level, if available. • If a patient is at the lowest dose of study drug, the drug may be held for ≤21 days to allow treatment and if the level returns to a grade 1 or lower, treatment can be resumed with a reevaluation monthly • See management of hyperlipidemia and hypertriglyceridemia and hyperglycemia below
Grade 2 hyperglycemia	• Adjust medications as medically appropriate and re-evaluate at next visit • If after medical adjustment grade 2 dysfunction persists, reduce dose to the next lower dose level, if available. • If a patient is at the lowest dose of study drug, the drug may be held for ≤21 days to allow treatment and if the level returns to a grade 1 or lower, treatment can be resumed with a reevaluation monthly • See management of hyperglycemia below

Toxicity	Action
Grade 3 or higher hyperglycemia or hypertriglyceridemia or hyperlipidemia	• Discontinue study drug permanently
Grade 3 or higher clinical liver failure (asterixis or encephalopathy/coma)	• Discontinue study drug permanently
Grade 3 or higher skin toxicity	• Discontinue study drug permanently
Grade 3 or higher Diarrhea	• Discontinue study drug permanently
Any other grade 3 toxicity	• 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 21 days.
Recurrence of a grade 3 toxicity after dose reduction	• Reduce dose to the next lower dose level, if available.
Any other grade 4	• Discontinue study drug permanently

6.3.3. Hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, ≥ 50x109/L)	• No action
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x109/L)	• Interrupt everolimus until resolution to grade ≤1 • If resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. • If resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x109/L)	• Discontinue study drug permanently

Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x109/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 occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	• Discontinue study drug permanently
Febrile neutropenia	• Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.
Recurrence of grade 3 toxicity after dose reduction	• Reduce dose to the next lower dose level, if available.

6.3.4. Non-infectious Pneumonitis

Worst grade pneumonitis	**Required investigations**	**Management of pneumonitis**	**Everolimus dose adjustment**
Grade 1	CT scans with lung windows.	No specific therapy is required	Stop study drug permanently.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O2 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 stop study drug permanently.
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 stop study drug permanently.
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 stop study drug permanently..

6.4. **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[17].

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).

6.4.1. Hepatitis B Reactivation

In the case of reactivation of Hepatitis B even in the face of pre-study screening, the trial will be immediately terminated and appropriate Hepatitis B therapy initiated.

6.4.2. 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. While taking Everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and treatment will be permanently discontinued with everolimus. Referral for immediate and appropriate treatment will be made.

6.4.3. 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 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 prednisone (short course), topical corticosteroids, or pimecrolimus.

6.4.4. 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:

- All patients may elect to start an alcohol-free Dexamethasone oral solution 5mg/5ml that is commercially available. They may take 10 mL up to 4 times a day and swish in their mouth for 2 minutes after which they are to spit it out. This may be done as prophylaxis at the time of initiation of everolimus.
- 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. Patients may also use the above mentioned alcohol-free Dexamethasone oral solution 5mg/5mL that is commercially available.
- 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®).
- For Grade 3 (Symptomatic and Unable to adequately aliment or hydrate orally, temporary dose interruption until recovery to ≤ Grade 1. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
- Antifungal agents should not be used, other than topic creams and ointments, including vaginal preparations. If a need arises for a systemic anti-fungal agent, the patient must come off study permanently.

6.4.5. Diarrhea

Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea). .

6.4.6. Hyperlipidemia, Hypertriglyceridemia and Hyperglycemia

Treatment of hyperlipidemia and hypertriglyceridemia should take into account the pre-treatment status and dietary habits of the patient. Grade 1 hypercholesterolemia or hypertriglyceridemia may be treated at the discretion of the provider with diet therapy or medications such as fibrates and an HMG-CoA reductase inhibitors. Grade 2 hypercholesterolemia or hypertriglyceridemia will further lead to a one level dose reduction as well as additional therapy with diet and medications as above.

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 creatinine 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. Hemoglobin A1C will be checked prior to study initiation and glucose will be monitored during the study. Hyperglycemia should be treated in standard clinical fashion.

6.4.7. 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 will have drug permanently discontinued.

Individuals participating in this trial will need to be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with lung toxicity. In addition, pulmonary function tests (PFTs) and CT of the chest will be conducted, if clinically indicated, to monitor for pneumonitis. If any grade non-infectious pneumonitis develops, the patient will be taken off study.

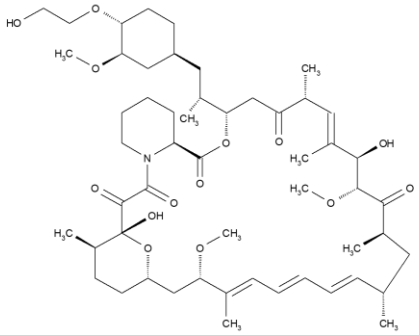
6.5. **Fertility**

The potential for everolimus to cause infertility in male and female patients is unknown. However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed. Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

7.0 Study Agent Information

7.1. Everolimus Formulation, Product identification, Package and Labeling

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



Everolimus (RAD001) is a selective mammalian target of rapamycin (mTOR) inhibitor, specifically targeting the mTOR-raptor signal transduction complex 1 (mTORC1). mTOR is a key serine-threonine kinase in the PI3K/AKT/mTOR signaling cascade, a pathway known to be dysregulated in the majority of human cancers and TSC. Everolimus exerts its activity through high affinity interaction with the intracellular receptor protein FKBP12. The FKBP12/everolimus complex binds to mTORC1, inhibiting its signaling capacity. mTORC1 signaling is affected through modulation of the phosphorylation of downstream effectors, the best characterized of which are the translational regulators S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4E-BP). Disruption of S6K1 and 4E-BP1 function, as a consequence of mTORC1 inhibition, interferes with the translation of mRNAs encoding pivotal proteins involved in cell cycle regulation, glycolysis and adaptation to low oxygen conditions (hypoxia). This inhibits tumor growth and expression of hypoxia-inducible factors (e.g. HIF-1 transcription factors); the latter resulting in reduced expression of factors involved in the potentiation of tumor angiogenic processes (e.g. the vascular endothelial growth factor VEGF). Everolimus is a potent inhibitor of the growth and proliferation of tumor cells, endothelial cells, fibroblasts and blood vessel-associated smooth muscle cells. Consistent with the central regulatory role of mTORC1, everolimus has been shown to reduce tumor cell proliferation, glycolysis and angiogenesis in solid tumors in vivo, and thus provides two independent mechanisms for inhibiting tumor growth: direct antitumor cell activity and inhibition of the tumor stromal compartment.

Everolimus is formulated as tablets for oral administration of 5mg and 10mg strength.

7.2. Availability

Everolimus will be supplied for this protocol by Novartis. .

7.3. Drug Ordering, Storage and Handling

Following submission and approval of the required regulatory documents, participation in the study initiation meeting and receipt of the site activation letter from the CTO Regulatory Coordinator, the initial order may be placed. Drugs will be ordered by contacting the study monitor as listed on the cover page of this protocol.

Everolimus 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. Refer to label for expiration date and storage conditions.

It may be necessary to ensure that patients have enough medication for the built-in evaluation and visit windows throughout study treatment (+/- 5 days).

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

7.4. Destruction of Drug

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified.

7.5. Records to be kept at Site; Dispensing and Accountability

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of person responsible for each investigational product inventory entry/movement.
- Amount dispensed to and returned by each patient, including unique patient identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).

8.0 Study Calendar

	Screening [A]	Day 1 of Cycles 1, 3, and 5 [H]	Day 1 of Cycles 2, 4, and 6 [H]	Cycle 5 Day 1 [H]	Cycle 6 Day 28 [H]	Off Treatment	12 Month Follow-up [H]
Informed Consent	X						
Medical History	X						
Concurrent Medications	X	X	X			X	
Height	X						
Weight	X	X	X			X	
Physical exam	X	X	X			X	
Vital signs [B]	X	X	X			X	
ECOG Performance Status	X	X	X			X	
Serum chemistry [C]	X	X	X			X	
FKSI QOL Assesment	X	X	X			X	X
CBC w/diff, plts	X	X	X			X	
Fasting serum cholesterol & Triglycerides & Hgb A1c	X	X				X	
EKG	X						
Hepatitis B, Hepatitis C & HIV Screening [D]	X						
Tumor Measurements	X			X	X		X
Optional Correlative Tissue Collection		X [E]	X [F]				
Optional Correlative Serum Collection		X [E]		X	X		X
Serum Pregnancy Test [G]	X						
Urine or Serum Pregnancy Test [G]		X	X			X	
Adverse Event Assessment		X	X				

A: Screening H&P, EKG and all labs must be ≤ *14 days* prior to registration.
Tumor measurements and radiologic evaluations must be ≤ *30 days* prior to registration.
Pre-study assessments may be used for cycle 1 day 1

B: Screening blood pressure must be assessed with three measurements at approximately 2-minute intervals.

C: Serum chemistry includes Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, fasting glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, glucose.

D: Screening for Hepatitis B will include, HBsAg, HBsAb, and HBc Ab. A positive HBsAb result in patients who have received prior HBV vaccination will not lead to exclusion from the study as long as HBsAg is negative.
Screening for Hepatitis C will be via Hepatitis C antibody. If positive confirmation with quantitative RNA PCR will be done.

E: If archival tissue is available from a previous renal lesion biopsy, unstained slides will be collected as detailed in 5.5. Correlative blood and tissue for this timepoint will be collected at Cycle 1 Day 1 only.

F: If a percutaneous intervention or surgical intervention is performed during the study, tissue will be collected for further analysis as detailed in 5.5

G: Women of Childbearing Potential Only. Serum pregnancy test at time of screening must be completed **<72 hours** before registration

H: All study visits have a window of +/- 5 days. Ensure that patients are given enough study drug to last until their next visit if scheduled more than 28 days from start of a cycle.

9.0 Adverse Events

9.1. Definitions

9.1.1. Adverse event (AE)

An adverse event is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*.

9.1.2. Serious Adverse Event (SAE)

A serious adverse event is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

9.1.3. Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

- Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
- Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE

9.1.4. Attribution/Relationship to study drug

- Definite – clearly related
- Probable – likely related
- Possible – may be related
- Unlikely – doubtfully related

- Unrelated – clearly not related

9.1.5. Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

- The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or
- The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event.

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

Adverse event monitoring should be continued for at least 30 days or five half-lives (whichever is longer) following the last dose of study treatment.

10.0 Recording and Reporting Responsibilities

10.1. Site Recording responsibilities:

Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

All SAEs will be recorded on the FDA MedWatch form 3500a. The principal investigator has the obligation to report all serious adverse events to the FDA (if applicable), IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E). .

10.2. Site Reporting responsibilities:

1) The investigator/ site is responsible to report all SAEs that occur on or after the first day of study treatment to the sponsor within 24 hours of becoming aware of the event. All subsequent SAEs must be reported for up to 30 days after the last treatment.

   Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be

reported to the IRB at their discretion. Copies of events reviewed by the IRB must be sent by email to SAE.FCCC@fccc.edu.

2) If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the OCR, draft revisions will be made in track changes and submitted to the OCR for consideration. Any consent revisions must receive OCR approval prior to submission to the IRB.

3) Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the Study Monitor for confirmation with the Sponsor-Investigator.

4) If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

5) Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in the trial master file.

The participating site should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

10.3. **Sponsor Reporting Responsibilities:**

1) Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2) If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the ISRU for each site's IRB of record along with the report of the adverse event.

3) Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study within the OCR.

4) SAEs that are related, unexpected, fatal, or life-threatening are reportable through the Food and Drug Administration (FDA) MedWatch program by telephone or fax no later than 7 calendar days after initial receipt of the information. Further information on the timing of submissions is as directed by FDA guidelines (www.fda.gov/medwatch/index.html). Serious, unexpected events that suggest significant clinical risk will be submitted to within 15 calendar days after initial receipt of this information.

   Food and Drug Administration:
   Telephone 1-800-332-1088
   Fax 1-800-332-0178
   http://www.fda.gov/medwatch/report.htm

5) The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours..

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

10.4. Pregnancy

All WOCBP must be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Site Investigator must immediately notify the Fox Chase Cancer Center Study Monitor, who will notify Dr. Robert Uzzo, MD; the study PI. Novartis will also be notified by the FCCC CTO within 24 hours.

The study drug will be immediately discontinued. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The newborn will be followed for at least 12 months.

11.0 Measures of Effect

11.1. Response Evaluation Utilizing DCE-MRI

DCE-MRI assessments will be performed at baseline, on Cycle 5 Day 1, on Cycle 6 Day 28, and 12 months after the start of treatment. The Cycle 6 Day 28 MRI and the 12 month MRI will be done even if patient doesn't continue onto cycles 5 and 6.

Location and size of the IV, as well as type and amount of contrast and injection rate should be the same for all time points of each individual patient. These can be different between patients.

Protocol should contain at minimum breathhold axial T1W in and out of phase multiplanar gradient echo sequence. To evaluate volume of the index lesion perform axial and coronal breathhold T1W 3-d gradient echo sequences with and without fat saturation (VIBE, LAVA/FAME and THRIVE for Siemens, GE and Philips respectively). Then, dynamic pre and post contrast enhanced nonbreathhold coronal T1W fast 3-d gradient echo sequences to run for two minutes. Each individual volume acquisition time should be maximum 4-5 seconds. These should be lower resolution with 5 mm slice thickness and adjust slice number to cover the size of the index lesion usually 15-20 slices. Phase encoding of 128 or less to keep acquisition time of less than 5 seconds. Patients should be instructed to perform shallow breathing. Start injection of the contrast 15 seconds after the start of the acquisitions. Acquisitions stop at 2 minutes after the start and at 2.5 minutes repeat the coronal and axial breathhold T1W fast 3-d gradient echo sequences with fat sat in that order.

Choose a central slice of the index lesion on the pre and post coronal breathhold images and trace the perimeter and get a signal intensity number for both. If possible choose a slice with a large soft tissue component and trace that separately re and post. Calculate a percent enhancement as follows: (Post – Pre/Pre) x 100. Dynamic data can be used to choose post time point with maximum enhancement. If possible, calculate an AUC 45 (area under the curve for 45 seconds) from the dynamic data. Volumes can be calculated on the breathhold 3-d sequences with or without fat sat. If dynamic sequences are unusable secondary to artifacts, then percent enhancement can be calculated from the breathhold 3-d T1W sequences with or without fat sat.

11.2. Methods for Evaluation of Disease

ROI's should be drawn around the solid nonfat portions of the tumor. One should evaluate signal intensity on arterial and portal venous phase images using identical delay times after start of injection for each time. For the exploratory objective 2.3.1, principles of Choi response criteria should be use (measure AUC for first 30 seconds post injection).

11.3. Response Criteria

Patients who have ≥25% decrease in tumor volume after 4 cycles of everolimus therapy will continue study drug for 2 additional cycles. Those with < 25% reduction or a new lesion (defined at 1 cm in longest diameter or more) will be taken off treatment.

11.4. Health Related Quality of Life

Health-related quality of life will be assessed with the use of patient responses to the 19-item Functional Assessment of Cancer Therapy (FACT) Kidney Symptom Index (FKSI-19; on a scale from 0 to 76, with higher scores indicating fewer symptoms)[18] (Appendix III). The instruments will be administered at baseline, on day 1 of each 28 day cycle, at study drug discontinuation and at the final study visit.

11.5. Serum Corrrelatives

PBMC, serum and plasma will be collected at baseline to look for evidence of mTOR inhibition – seeing an increase in pAKT and a decrease/inhibition of pS6—as well as future research like plasma RNA (nanostring panel) and cfDNA. For cfDNA blood will be collected at a single time point using either two 7ml STRECK tubes per patient (if cannot be frozen immediately) or frozen as per the lab manual. cfDNA will be extracted using QIAamp circulating nucleic acid kit and stored for future use.

12.0 Statistical Considerations

12.1. Study Design/Endpoints

The required sample size for this trial is 43 patients, using a Simon two-stage design. The sample size justification and details are below.

We will conduct a single arm Phase II study to assess the efficacy of everolimus in patients with ≥3cm sporadic AMLs. Response for a patient will be defined by a decrease in size of ≥25% after 4 cycles of treatment.

We will implement an optimal two-stage Simon design for this trial. The new treatment would be of interest if the proportion, p, of responding patients is at least 25%. A proportion of patients with a response rate of less than 10% will be of no interest. Forty three (43) patients will allow us to test the null hypothesis: $p \leq 10\%$ against the alternative hypothesis: $p \geq 25\%$ at the 5% level of significance (α) with 80% power for a one-sided test. The early stopping point is 18 patients for both efficacy and toxicity. For efficacy, if 2 or fewer patients respond among the first 18 patients then the null hypothesis will not be rejected and the trial will be terminated. The probability of early stopping under the null is 73%. If the trial progresses until 43 patients are evaluated and 8 or more patients respond, then the null hypothesis will be rejected.

For toxicity, the trial will be paused and termination considered if out of the first 18 patients, 3 or more come off trial due to any adverse events as defined in the protocol. If the study proceeds to stage II (total enrollment = 43 patients), the trial will be paused and termination considered if at any point 8 or more patients come off trial due to any adverse events as defined in the protocol. If the true rate of any adverse events necessitating a patient to come off trial is 20%, the probability of early stopping is 73%; if the true rate of any adverse events necessitating a patient to come off trial is 5%, the probability of early stopping is 6%. Pause and

termination consideration for toxicity will occur, either early or finally, with probability 81% if true toxicity proportion is 20%; and 6% if it is 5%.

To ensure oversight with respect to toxicity, an interim review will be conducted if the early stopping rule for toxicity is reached in the first 18 patients. For this interim review, all available data related to primary and secondary efficacy and toxicity endpoints will be collected, summarized and presented. The data will be reviewed at a meeting of the invested trial parties, including but not limited to investigators at all participating sites (PIs or representatives at outside centers may call in to the meeting), staff on the research team, members of the FCCC Investigator Sponsored Research Unit, and statistics team. A summary recommendation will emerge from the meeting as to whether the study should be terminated or modified to a new dosing schema. This recommendation will be forwarded to the FCCC DSMB for signoff. Study accrual will halt until the outcome of the interim review is accepted by the FCCC DSMB. If the DSMB does not concur with the findings of the Investigator Meeting, the local FCCC IRB will review the trial for final decision.

In secondary analyses we will use graphs, standard descriptive statistics (mean, median, minimum, maximum, standard deviation, two-sided 95% confidence intervals) and Generalized Estimating Equation methods to characterize and model longitudinal health-related quality of life (HRQoL) measurements. Tumor regrowth kinetics will be characterized by the percent change in volume from the date of everolimus treatment termination. Values will be summarized using plots and standard descriptive statistics (mean, median, minimum, maximum, standard deviation, two-sided 95% confidence intervals) separately for each measurement following treatment discontinuation. Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths and laboratory abnormalities. Spearman's correlation coefficients will be computed to estimate the association between the largest percentage volumetric response from baseline with levels of perfusion/angiogenic content/vascularity of baseline tumor as measured by DCE MRI.

We will tabulate the frequencies of all grade 2 or higher adverse events as defined by NCI CTCAE version 4 criteria. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

12.2. Sample Size/Accrual Rate

This study will require the enrollment of 43 evaluable participants over a 24 month period, or an approximate average of 2 participants per month for 2 years. The study is planned to be amended in the future for additional 2-4 sites to help increase accrual.

13.0 Data and Safety Monitoring Plan

13.1. Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the Sponsor-Investigator who will review these data on a regular basis at a rate dependent on subject accrual.

All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and Sponsor-Investigator as applicable.

13.2. Data Safety Monitoring Board

Interim analysis of toxicity, outcome and ongoing scientific investigations will be performed at least by the Fox Chase Cancer Center Data Safety Monitoring Board (FCCCDSMB). In this capacity the FCCCDSMB will serve as an advisory committee to the Sponsor-Investigator. The FCCCDSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Sponsor-Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Sponsor-Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

14.0 Administrative

This study will be conducted in accordance will local, state, and Federal regulations and according to accepted good clinical practice guidelines.

14.1. Data Reporting

The FCCC Study Monitor will request case report form submission upon resolution of outstanding queries. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit. Participating sites are responsible for submitting case report forms to the Study Monitor within two weeks of request.

The ISRU is responsible for compiling and submitting data to the Sponsor-Investigator and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in a secure location.

The ISRU is responsible for distributing and tracking review of all IND Action Letters, Safety Reports, study specific Serious Adverse Events

14.2. Retention of Records

Time points for the retention of records are described in detail in the contract between the grantor and the OCR and passed on to the participating site. Please refer to the study specific terms for specific time points. In all cases the Study Monitor must be notified of any plans to move records to an offsite location prior to doing so.

14.3. **Study Agents**

Any study agent supplied through the OCR from the manufacturer or a third party distributor may not be used for any purpose outside the scope of this protocol. The agent may not be transferred to any party not participating in the clinical trial.

14.4. **Informed Consent**

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study.

The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language. Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

Appendix I: NYHA Classification

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Appendix II: Child-Pugh Criteria

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Appendix III: FACT FKSI-19 Questionnaire

NCCN-FACT FKSI-19 (Version 2)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	C2	I am losing weight	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	B1	I have been short of breath	0	1	2	3	4
	BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
	BP1	I have bone pain	0	1	2	3	4
	L2	I have been coughing	0	1	2	3	4
	HI12	I feel weak all over	0	1	2	3	4
	RCC 2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GH6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	GF1	I am able to work (include work at home)	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale

English (Universal)

03 March 2010
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Appendix IV: Novartis SAE Fax Covers

Commented [CM1]: Please use updated SA# Suspected/Non Suspect Coverage, version 3, Mar 2017, on the attached email.

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Patient Safety via **1-877-778-9739**

If you experience difficulty faxing this form, please email the SAE & Cover Sheet to clinicalsafetyop.phuseh@novartis.com

Investigator contact details:

Fax number: _____

Phone number: _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

Version 3.0_14 Mar 2017

NOVARTIS

Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Patient Safety via **1-877-778-9739**

If you experience difficulty faxing this form, please email the SAE & Cover Sheet to clinicalsafetyop.phuseh@novartis.com

Investigator contact details:

Fax number: _____

Phone number: _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

This document contains important safety information.
If fax is received in error, please forward to 1-877-778-9739

Version 3.0, 14 Mar 2017

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