

Abbreviated Title: Phase II everolimus for BHD

NCI Protocol #: 15-C-0166 B

Version Date: March 7, 2017

Title: Phase 2 Study of Everolimus Therapy in Patients with Birt-Hogg-Dubé Syndrome (BHD)-Associated Kidney Cancer

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- A. Obtain information by intervening or interacting with living individuals for research purposes*
- B. Obtaining identifiable private information about living individuals*
- C. Obtaining the voluntary informed consent of individuals to be subjects*
- D. Makes decisions about subject eligibility*
- E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes*
- F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes*
- G. Some/all research activities performed outside NIH*

Commercial Agent: Everolimus/RAD001/Affinitor (supplied by Novartis)

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PRÉCIS

Background:

- Birt-Hogg-Dubé (BHD) is a hereditary cancer syndrome with clinical manifestations including cutaneous fibrofolliculomas, lung cysts/pneumothorax, and renal cell carcinoma (RCC). RCC occurs in approximately 30% of patients with BHD. It presents at an early age of onset and is commonly bilateral and multifocal.
- Tumors associated with BHD can have variable histology, however approximately 85% of these tumors have a chromophobe component (either alone or part of a hybrid tumor mixed with elements of oncocytoma).
- The current management includes surgical resection with partial nephrectomy when tumors reach 3 cm. While significant morbidity can be associated with repeat, partial nephrectomy with this approach, most patients can maintain renal function and do not develop systemic disease. There are no proven systemic therapy options for BHD to date.
- Germline mutations in the gene *Folliculin* (*FLCN*) are the genetic hallmark of BHD and can be found in greater than 90% of patients. *FLCN* is believed to function like a classic tumor suppressor gene with a second hit in the wild type allele (somatic mutation or loss of heterozygosity) occurring in the majority of renal tumors.
- BHD is in the family of hamartomatous disorders similar to TSC and Cowden Syndrome, and studies have found activation of the PI3K/mTOR pathway in BHD renal tumors. *FLCN* is believed to be part of a complex that interacts with AMPK and is involved with regulation of mTOR activity. *In vitro* and *in vivo* models of *FLCN* loss demonstrate activation of both mTORC1 and mTORC2.
- Preclinical data from conditional *FLCN* knockout mice demonstrate that treatment with sirolimus can reverse renal manifestations.
- We hypothesize that mTOR inhibition with everolimus treatment will be clinically active in BHD associated RCC.

Objectives:

- To determine the overall response rate with everolimus treatment in subjects with BHD-associated renal tumors.

Eligibility:

- Patients with renal cell carcinoma (RCC) associated with Birt-Hogg-Dubé Syndrome (BHD).

Design:

- This is an open label, phase II study to evaluate the efficacy and safety of everolimus therapy in patients with BHD associated renal tumors. Up to 16 evaluable patients will be enrolled.
- Tumor response rate will be measured by RECIST and efficacy analysis will be done.
- Secondary endpoints will evaluate growth rates (cm/year) while on therapy.
- Additionally, reduction in the size of lung cysts and cutaneous fibrofolliculomas will be evaluated.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the overall response rate with everolimus treatment in subjects with BHD-associated renal tumors.

1.1.2 Secondary Objectives

- 1.1.2.1 To study the safety and tolerability of everolimus in patients with BHD-associated localized renal tumors.
- 1.1.2.2 To assess changes in tumor growth rates and ability to delay surgical management in BHD patients.
- 1.1.2.3 To assess progression-free survival (PFS) and overall survival (OS).
- 1.1.2.4 To evaluate the effect of everolimus on mTOR activity in renal tumors (using pre- and on-treatment biopsies when available).
- 1.1.2.5 To assess the effect of therapy on BHD associated lung cysts and cutaneous fibrofolliculomas.

1.2 BACKGROUND AND RATIONALE

1.2.1 Overview of Birt-Hogg-Dubé (BHD) Syndrome

Birt-Hogg-Dubé (BHD) is a hereditary cancer syndrome characterized by a propensity to develop cutaneous fibrofolliculomas/trichodiscomas, lung cysts/pneumothorax, and renal cell carcinoma (RCC).¹ While fibrofolliculomas and lung cysts appear to be highly penetrant (affecting 70% or more patients), RCC occurs in approximately 12-34% of patients with BHD. It presents at an early age of onset (median age of onset around 50 years) and is commonly bilateral and multifocal.²⁻⁴ Renal tumors associated with BHD can have variable histology; however approximately 85% of these tumors have a chromophobe component (either alone or part of a hybrid tumor mixed with elements of oncocytoma).⁵ Clear cell RCC, papillary RCC and oncocytomas constitute the remainder of tumors. There is considerable variability in presentation and different members of a given family may present with dissimilar renal findings; furthermore, in any given individual, multiple histological variants of RCC can coexist. Microscopic foci of dysplastic cells defined as renal ‘oncocytosis’ have been observed in adjacent ‘normal’ kidney parenchyma in the majority of BHD patients who present with renal tumors independent of histology, thus suggesting that these oncocytic cells may be precursor lesions to hybrid oncocytic tumors as well as chromophobe and clear cell renal carcinomas.

The current management of BHD patients with renal tumors includes surveillance of small tumors with nephron-sparing surgical resection when tumors reach 3 cm.⁶ While significant morbidity can be associated with repeat, partial nephrectomy, with this approach, most patients can maintain renal function and do not develop systemic disease. Once individual tumors reach a size of 3 cm or more, there is an incremental increased risk of metastatic disease. Although metastatic disease is rarely encountered in clinical practice in appropriately managed patients,

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the disease is usually fatal once metastatic and there are no proven systemic therapy options for BHD to date.^{6,7}

Germline mutations in the *Folliculin* (*FLCN*) gene are the genetic hallmark of BHD and mutations or deletions of this gene can be found in greater than 90% of patients.^{8,9} The gene for BHD was localized to the short arm of chromosome 17 (17p) by genetic linkage analysis and was further identified by positional cloning.^{3,10,11} The gene consists of 11 coding exons, and mutations have been identified in all 11 exons. The majority of germline folliculin mutations are insertions/deletions, nonsense mutations or splice-site alterations that result in a truncated protein with loss of function.¹ More recently, partial deletions involving *FLCN* have been identified in the germline of BHD patients.

FLCN is believed to function like a classic tumor suppressor gene with a second hit in the wild type allele occurring in the majority of renal tumors. In a study of 77 BHD-associated renal tumors, sequence alteration were identified in over half the tumors, while in 17% of samples the second allele was lost as a result of LOH on chromosome 17.¹²

The exact function of folliculin and the mechanisms by which loss of function of this protein leads to renal tumors remain to be fully elucidated. However, recent studies have begun to provide some insight into the biochemical pathways involving folliculin. Co-immunoprecipitation experiments in cells overexpressing *FLCN* identified a novel *FLCN* interacting protein, FNIP1, that associates with *FLCN* through its C-terminus and interacts with 5'-AMP-activated protein kinase (AMPK), a kinase-competent complex that functions to monitor and maintain energy homeostasis in cells by negatively regulating mammalian target of rapamycin (mTOR), the master controller of protein synthesis and cell growth.^{13,14} Baba et al. showed that *FLCN* exists in multiple phosphorylated forms, which are dephosphorylated by different mechanisms (inhibition of mTOR signaling and inhibition of AMPK activity), suggesting the existence of phosphorylated *FLCN* residues that function to either inhibit or activate *FLCN* function, respectively.¹³ *FLCN* phosphorylation sites at serine 62 and serine 302 were identified, which appear to be differently regulated by the mTORC1-dependent pathway. FNIP1 expression enhances *FLCN* phosphorylation and both proteins can serve as direct or indirect substrates of AMPK.^{13,15} A second folliculin interacting protein, FNIP2, was subsequently identified. FNIP2 shares significant homology with FNIP1 and was shown to be a heterodimeric partner for both FNIP1 and *FLCN*.^{16,17}

Several lines of evidence from *Flcn*-deficient mouse models suggest that *Flcn* may modulate the AKT-mTOR pathway. Conditional inactivation of *Flcn* specifically in mouse kidneys resulted in the development of enlarged multicystic kidneys with hyperplastic cells protruding into the cystic lumen and cystic renal cell carcinomas that resulted in morbidity by 21 days of age due to renal failure.^{18,19} *Flcn*-deficient kidneys showed significant upregulation of mTOR activity as evidenced by activation of downstream effectors. Rapamycin treatment extended the lifespan and ameliorated the cystic kidney phenotype confirming that the AKT-mTOR pathway was activated in the *Flcn* knockout kidneys. In support of these data, *Flcn* heterozygous knockout mice developed solid renal tumors at median age of 23 months that displayed loss of the remaining *Flcn* allele and histologies similar to human BHD tumors. These tumors demonstrated activated phospho-AKT, phospho-mTORC1 and phospho-mTORC2.²⁰ Human BHD tumors also showed activated AKT-mTORC1 and AKT-mTORC2 pathways, supporting a role for *FLCN* in regulating AKT-mTORC1-mTORC2 signaling in human kidney.

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Based on these data, we hypothesize that mTOR inhibition with everolimus treatment will be clinically active in BHD associated RCC.

1.2.2 Introduction to investigational treatment using 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.

Afinitor® and was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafenib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. 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 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 hepatically impaired subjects have participated in the clinical pharmacology studies.

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

1.2.3 Overview of everolimus

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1-1, Figure 1-1). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers.²³

Everolimus is believed to act

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;

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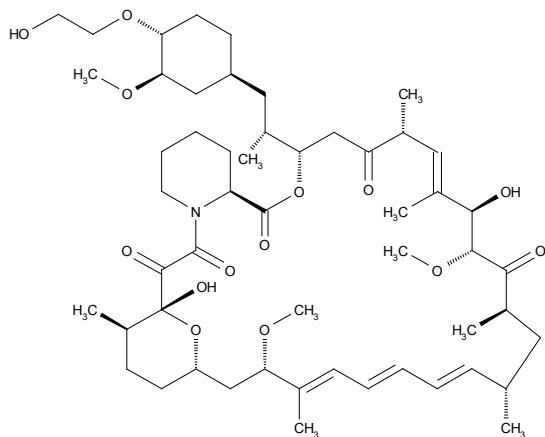
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- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Table 1-1: Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.0 ^{4,9}]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1-1: Chemical structure of Everolimus



1.2.3.1 mTOR pathway and cancer

At the cellular and molecular level, everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development.²⁴

The main known functions of mTOR include the following²⁵:

- 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^{26,27};
- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers²⁸;
- 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.

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1.2.3.2 Non-clinical experience

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

In vitro genotoxicity studies covering relevant genotoxicity end-points showed no evidence of clastogenic or mutagenic activity.

In male fertility studies in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg which corresponded to 0.7 times the estimated clinical exposure at 10 mg/day, and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus caused an increase of pre-implantation loss in female rats at doses > 0.1 mg/kg, suggesting it could also potentially impact fertility in females. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the planned therapeutic level comprising mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryo toxicity was evident by an increase in late resorptions. Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥ 0.1 mg/kg, and did not indicate a specific toxic potential.

The potential reproductive risk for humans is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the fetus. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore, women who are taking everolimus should not breastfeed.

Additional information about everolimus can be found in the Affinitor package insert.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have a clinical diagnosis of Birt-Hogg-Dubé Syndrome (clinical features consistent with BHD and /or a germline *FLCN* mutation) and the presence of localized, locally advanced or advanced, renal tumor(s).

2.1.1.2 Patients must have measurable disease, as defined by RECIST 1.1

2.1.1.3 Age ≥ 18 years.

2.1.1.4 ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$, see Appendix A, Section 13.1).

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

- leukocytes	$\geq 3,000/\text{mcL}$
- absolute neutrophil count	$\geq 1,500/\text{mcL}$
- platelets	$\geq 100,000/\text{mcL}$
- total bilirubin	$\leq 2\text{mg/dL}$
- AST(SGOT)/ALT(SGPT)	$\leq 2.5 \times$ institutional upper limit of

– creatinine OR – creatinine clearance – fasting serum cholesterol AND – fasting triglycerides	normal (≤ 5 x ULN in patients with liver metastases) $\leq 2.0 \times$ ULN ≥ 30 mL/min/1.73 m ² ≤ 300 mg/dL OR ≤ 7.75 mmol/L ≤ 2.5 x ULN
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NOTE: In case one or both of these thresholds (for fasting serum cholesterol or triglyceride) are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

- 2.1.1.6 No history of major bleeding, recent or active myocardial ischemia, GI perforation, cerebrovascular accidents or other significant illness.
- 2.1.1.7 Recovery from acute toxicity of prior treatment for RCC (to \leq grade 1 the active version of CTCAE or to a level permitted under other sections of Inclusion/ Exclusion criteria). Additionally, in patients who have received standard or experimental treatments for their RCC at least approximately 5 half-lives should have elapsed from the last dose at the time of study entry.
- 2.1.1.8 No prior therapy with an mTOR-pathway inhibitor.
- 2.1.1.9 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.2 Exclusion Criteria

- 2.1.2.1 Patients currently receiving anticancer therapies (including chemotherapy, radiation therapy, antibody based therapy, etc.).
- 2.1.2.2 Known intolerance or hypersensitivity to everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).
- 2.1.2.3 Patients with known brain metastases unless treated with an appropriate modality with no evidence of progression/recurrence for >3 months
- 2.1.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics, invasive fungal infection, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 2.1.2.5 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with everolimus. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral everolimus.
- 2.1.2.6 Uncontrolled diabetes mellitus as defined by HbA1c $>8\%$ despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM)

may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary.

2.1.2.7 Patients who have any severe and/or uncontrolled medical conditions such as:

- a. unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction \leq 6 months prior to start of everolimus, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease.
- b. Symptomatic congestive heart failure of New York heart Association Class III or IV.
- c. known severely impaired lung function (spirometry and DLCO 50% or less of normal and O₂ saturation 88% or less at rest on room air).
- d. active, bleeding diathesis.

2.1.2.8 Chronic (treatment $>$ 1 month) or ongoing treatment with corticosteroids or other immunosuppressive agents. Topical or inhaled corticosteroids are allowed.

2.1.2.9 Patients who have received live attenuated vaccines within 1 week of start of everolimus
Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

2.1.2.10 Patients, who in the opinion of the investigator, are unlikely to comply with follow-up visits or other study requirements. Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing.

2.1.2.11 Pregnant or nursing (lactating) women.

2.1.2.12 Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, who do not agree to use highly effective methods of contraception during the study and 8 weeks after.

Highly effective contraception methods include combination of any two of the following:

- a. Use of oral, injected or implanted hormonal methods of contraception or;
- b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
- d. Total abstinence or;
- e. Male/female sterilization.

Women are considered post-menopausal and not of child-bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to randomization. In the case of oophorectomy alone, only when the reproductive status of the woman

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has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

2.1.2.13 Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment.

2.1.2.14 Prior invasive malignancy of other histology currently requiring treatment.

2.1.2.15 Patients with active Hepatitis B (detectable HBV-DNA or HBsAg +) or Hepatitis C infection (detectable HCV RNA by PCR)

2.1.2.16 Patients who are currently on or have used potent or moderate inhibitors or strong inducers CYP3A4 or PgP inhibitors in the past 2 weeks

2.2 SCREENING EVALUATION

Screening evaluations must be performed within the timeframes indicated below. Screening procedures may be performed on an NIH screening protocol or the UOB 02-C-0159. Imaging studies may also be performed at an outside institution for expedience. If procedures are performed on this treatment protocol, the screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

- To be performed within 2 weeks prior to subject receiving study drug
 - History and physical evaluation
 - Vital signs
 - Performance status
 - EKG
 - Hematology: CBC with differential
 - Biochemistry: BUN or uric acid, creatinine, LDH, total protein, sodium, potassium, calcium, total bilirubin, GGT, albumin, alkaline phosphatase, AST, fasting glucose
 - Fasting serum lipid profile
 - Urinalysis
 - CT chest/abdomen/pelvis and/or CT chest plus MRI abdomen/pelvis, bone scans in patients with known or suspected bone metastases
 - CT Neck in patients with known or suspected metastatic disease in the neck
 - Brain MRI or Brain CT (studies are to be performed with contrast unless renal impairment or allergy prohibits the use of contrast)
 - FDG-PET in patients with known or suspected metastatic disease
 - Serum β HCG (in female patients of childbearing potential)
 - HbA1c, pulmonary function tests (if clinically indicated), pulse oximetry
 - HBV-DNA, HBsAg, HBs Ab, HBc Ab, HCV-RNA-PCR

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The management guidelines, in Section [3.3.2](#), are provided according to the results of the baseline assessment of viral load and serological markers for hepatitis B.

The management guidelines, in Section [3.3.2](#), are provided according to the results of the baseline assessment of hepatitis C viral load.

For baseline evaluations, please see Section [2.4](#).

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-1@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 BASELINE EVALUATION

Baseline procedures need not be repeated if they have been performed within the appropriate screening timeframe (See Section [2.2](#)).

- Height
- Weight
- Thyroid function tests
- Prothrombin time/partial thromboplastin time (PT/PTT)
- Serum β hCG (in female patients of childbearing potential) within 2 weeks.
- CBC with differential.
- Total and direct bilirubin, AST/SGOT, ALT/SGPT, acute care panel, albumin, calcium, magnesium, LDH, amylase, lipase, lipid panel, T3, free thyroxine, TSH
- PFT
- Biopsies (optional) for correlative studies (see Section [5.1](#))
- Obtain archival tumor tissue when available (tissue block and/or up to 30 unstained slides)
- Photographic evaluation of skin lesions (only in patients with BHD- associated cutaneous)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open label, phase II study to evaluate the efficacy and safety of everolimus therapy in patients with BHD. Up to 16 evaluable patients will be enrolled.

Patients with BHD typically have bilateral, multifocal tumors localized to the kidneys. In general, the growth rates of these tumors is relatively slow and they are not expected to pose a risk of metastatic spread when the size of the tumors is <3cm. Most of these patients have a surgical option (partial nephrectomy) and are less willing to accept side effects than are patients with metastatic disease. Therefore, everolimus will be administered at a starting dose of 5mg PO QD. If the following criteria are met at the time of the first restaging evaluation, the dose will be escalated to 10mg PO QD.

- A) The patient has not had a complete or partial response, and
- B) The patient has not experienced grade 2 or greater toxicity attributable to everolimus

Restaging will be performed approximately every 12 weeks. Treatment can continue for up to 52 weeks in the absence of unacceptable toxicity or disease progression, except in patients with metastatic RCC associated with BHD in whom everolimus will be continued until disease progression or unacceptable toxicity.

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

3.2 DRUG ADMINISTRATION

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

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

The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. 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 until the tablet(s) is fully disintegrated (approximately 7 minutes), 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 contact the study center as soon as possible to ask for advice.

Patients should be instructed to take the study drug as per protocol and instructed to complete the medication diary found in Appendix B, Section **13.2**. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded appropriately.

3.3 DOSE MODIFICATIONS

3.3.1 Dose modification and dose delay

3.3.1.1 Dosing 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.

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All dose modifications should be based on the worst preceding toxicity. Dose modifications will be made only for those AEs thought to be related to everolimus.

For each patient, once a dose reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with everolimus. Dose modifications will follow the scheme outlined in Table 3-1. No more than 2 dose reductions will be allowed per patient.

Table 3-1: Study treatment schedule adjustments and dose levels

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

* Once patients have had a dose escalation to the 10mg p.o. QD dose, dose reductions for AEs will be to move to the next lower dose level.

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.

Table 3-2 and Table 3-3 list the dosing guidelines for everolimus-related non-hematologic and hematologic toxicities.

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Table 3-2: Dosing guidelines for everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Please refer to Table 3-4.
AST or ALT elevation	Maintain current dose level
Grade 1 (> ULN - 3.0 x ULN)	
Grade 2 (> 3.0 - 5.0 x ULN)	
AST or ALT elevation	Interrupt everolimus administration until resolution to \leq grade 1 (or \leq grade 2 if baseline values were within the range of grade 2). If resolution occurs \leq 7 days, everolimus should be re-started at the dose level prior to interruption.
Grade 3 (> 5.0 - 20.0 ULN)*	If resolution takes $>$ 7 days, or if event recurs within 28 days, hold everolimus until recovery to \leq grade 1 or baseline grade / value and reintroduce everolimus at one dose level lower, if available.
AST or ALT elevation	Discontinue everolimus.
Grade 4 (> 20 x ULN)*	
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 3.3.2.6)	Interrupt everolimus administration until resolution to \leq grade 1 or baseline grade / value. If resolution occurs within \leq 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 \leq 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 \leq grade 1 or baseline grade / value within 28 days.
Any other grade 4	Discontinue everolimus.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue everolimus
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 2.5 mg daily. Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation
Any non-hematologic toxicity requiring Everolimus interruption for $>$ 28 days	Discontinue everolimus

Table 3-3 Dosing guidelines for everolimus-related hematologic toxicities

Toxicity	Action
≤ Grade 2 thrombocytopenia (platelets <75, ≥ 50 x10 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 occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x10 ⁹ /L)	Discontinue everolimus
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 occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Discontinue everolimus
Febrile neutropenia	Interrupt everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued.
*Any hematologic toxicity requiring everolimus interruption for > 28 days	Discontinue everolimus

3.3.2 Management of specific toxicities

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

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

3.3.2.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections,

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such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus. Treat pre-existing infections prior to starting treatment with everolimus. While taking everolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

3.3.2.2 Management of skin toxicity

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

3.3.2.3 Renal Failure Events

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

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

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3.3.2.4 Management of stomatitis / oral mucositis / mouth ulcers

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

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

3.3.2.5 Management of diarrhea

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

3.3.2.6 Management of hyperlipidemia and hyperglycemia

Adverse Drug Reaction	Severity	Everolimus Dose Adjustment and Management Recommendations
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate everolimus at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue everolimus and treat with appropriate medical therapy.

3.3.2.7 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.

If non-infectious pneumonitis develops, the guidelines in Table 3-4 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 3-4: Management of non-infectious pneumonitis

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to Grade ≤ 1. Re-initiate everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days.
Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O ₂ indicated)	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O ₂ saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating everolimus at one dose level lower (approximately 50% lower than the dose previously administered depending on individual clinical circumstances) Discontinue everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation
Grade 4 (Life-threatening, ventilatory support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O ₂ 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.

3.3.2.8 Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy.²⁹ Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality.³⁰ A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Monitoring and prophylactic treatment for hepatitis B reactivation

Table 3-5 provides details of monitoring and prophylactic therapy according to the screening results of viral load and serologic markers testing.

Table 3-5: Action to be taken based on screening hepatitis B results

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV vaccination
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Pt will not be eligible for study		No prophylaxis Monitor HBV-DNA approximately every 3-4 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of everolimus. For HBV reactivation definition and management guidelines, see Table 3-6.

Table 3-6: Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBsAb (with no prior history of vaccination against HBV), OR positive HBcAb]	Treat : Start first antiviral medication AND Interrupt everolimus administration until resolution: <ul style="list-style-type: none"> • \leq undetectable (negative) HBV-DNA levels If resolution occurs within ≤ 28 days , everolimus can be re-started at one dose lower, if available (see Table 3-1 for dose levels available). If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of everolimus. If resolution occurs > 28 days Patients should discontinue everolimus but continue antiviral therapy at least 4 weeks after last dose of everolimus.

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

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Monitoring for hepatitis C flare

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

- Patients known to have a history of HCV infection, despite a negative viral load test at screening (including those that were treated and are considered ‘cured’)

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 3-7.

Table 3-7: Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 4.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

3.4 STUDY CALENDAR

1 cycle = 28 days

Evaluations below may be performed within \pm 3 days of indicated time in order to accommodate patient schedules, holidays and weather emergencies. Imaging studies and optional tumor biopsies may be performed within \pm 7 days of indicated time.

Baseline and Restaging evaluation will be performed at the NIH CC. However, mandated laboratory studies and other evaluations may be performed at local laboratory or by local health care providers.

Restaging will be performed approximately every 12 weeks. Treatment can continue for 52 weeks in the absence of unacceptable toxicity or disease progression.

Patients with BHD associated tumors localized to the kidneys will be treated for one year in the absence of unacceptable toxicity or disease progression. Patients with locally advanced or metastatic disease will be treated until disease progression in the absence of unacceptable toxicity.

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	Screening / Baseline	Day 1	Cycle 1 Day 14	Cycle 2 Day 1	Cycle 2 Day 14	Cycle 3 Day 1	Cycle 3 Day 14	Cycle 4 Day 1	Start of Every Cycle	EOT	Follow up ¹¹	Survival ¹²
Visit no.	1	2	3	4	5	6	7	8	9, 10 etc...		EOT + 28 days	
Treatment days	-14 to -1											
Demography/informed consent	X											
Relevant medical history/current medical conditions	X											
Diagnosis and extent of cancer	X											
Vital signs	X	X*		X		X		X	X	X		
Height	X											
Weight	X	X*		X		X		X	X	X	X	
Physical examination	X ⁸											
ECOG/Karnofsky performance status	X	X*										
EKG ¹	X											
Thyroid function tests	X		Every 12 weeks									
CBC with differential	X		X	X		X		X	X	X	X	
Serum Chemistries ²	X		X	X		X		X	X	X	X	
Fasting serum Lipid Profile ³	X			X		X		X	X	X		
Urinalysis ⁴	X			X		X		X	X			
Serum β hCG (in female patients of childbearing potential)	X			X		X		X	X			
HbA1c, pulse oximetry	X											
PT/PTT	X											

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	Screening / Baseline	Day 1	Cycle 1 Day 14	Cycle 2 Day 1	Cycle 2 Day 14	Cycle 3 Day 1	Cycle 3 Day 14	Cycle 4 Day 1	Start of Every Cycle	EOT	Follow up ¹¹	Survival ¹²
Visit no.	1	2	3	4	5	6	7	8	9, 10 etc...		EOT + 28 days	
Treatment days	-14 to -1											
Prior/concomitant medications	X											
Adverse events												
Tumor evaluation												
PFT	X											
CT chest/abdomen/pelvis and/or, CT chest plus MRI abdomen/pelvis ⁵	X									X		
CT Neck in patients with known or suspected metastatic disease in the neck ⁶												
CT or MRI for Brain	X											
Bone scans in patients with known or suspected bone metastases ⁷	X ⁸											
FDG-PET in patients with known or suspected metastatic disease	X ⁸											
Optional biopsy (At baseline, archival tumor samples may be used)	X						X					
Everolimus Dosing		Daily										
Follow up survival contact												X
HBV-DNA, HBsAg, HBs Ab, HBc Ab, HCV-RNA-PCR, ANTI- HCV ⁹	X											
HBV DNA ¹⁰									Every 3 - 4 weeks		X	X

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	Screening / Baseline	Day 1	Cycle 1 Day 14	Cycle 2 Day 1	Cycle 2 Day 14	Cycle 3 Day 1	Cycle 3 Day 14	Cycle 4 Day 1	Start of Every Cycle	EOT	Follow up ¹¹	Survival ¹²												
Visit no.	1	2	3	4	5	6	7	8	9, 10 etc...		EOT + 28 days													
Treatment days	-14 to -1																							
HCV RNA-PCR ¹⁰				Every 4 – 8 weeks						X	X													
Photographic evaluation of skin lesions ¹³	X	Every 12 weeks																						
All attempts should be made to complete the visits within 72 hours of the day indicated on the evaluation schedule. Visit 2 must be conducted no more than 21 days after the screening visit and 28 days for patient positive for HepB and C.																								
*If clinically indicated.																								
1. Screening ECG is a standard 12 lead and must be performed within 14 days of first dose for patients enrolled and may be repeated at the investigator's discretion if clinically indicated																								
2. Serum Chemistry must include: Albumin, Alkaline phosphatase, ALT (alanine transaminase), AST (aspartate aminotransferase), BUN (blood urea nitrogen), Calcium, Serum chloride, CO2 (carbon dioxide), Creatinine, Direct bilirubin, Gamma-GT (gamma-glutamyl transpeptidase), Glucose test, LDH (lactate dehydrogenase), Phosphorus, Potassium test, Serum sodium, Total bilirubin, Total cholesterol, Total protein, Uric acid.																								
3. Serum fasting lipid profile must include: total cholesterol and triglycerides. Patients should be in fasting state.																								
4. Standard urinalysis dipstick assessment must include: protein, glucose, blood, ketones, and leukocytes.																								
5. Chest, abdomen, pelvis scans need to be repeated at each tumor assessment visit (including if negative at baseline). Scans for complete and partial responses must be repeated at least at 4 weeks but no later than the next scheduled tumor assessment following the first documented response. Skin lesions should be photographed in addition to measuring.																								
6. CT Neck in patients with known or suspected metastatic disease in the neck will be repeated at restaging if positive for metastasis.																								
7. A bone scan or skeletal survey is to be performed at baseline and will be repeated at restaging if positive for metastasis.																								
8. Repeat at restaging only if indicated																								
9. All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C as outlined in Sections 2.2. Patients with viral hepatitis B or C risk factors should be screened for Hep B and HCV RNA-PCR.																								
10. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA every 3 – 4 weeks. Patients with positive HCV-RNA PCR or a history of past infection, even if treated and considered 'cured' – should be followed by HCV-RNA PCR every 4 – 8 weeks.																								
11. Follow up visits conducted at the EOT+28 days visit.																								
12. After progression, an attempt will be made to follow patients to obtain information about survival every three to six months.																								
Legend: wks stands for weeks, EOT for End of Treatment visit																								
13. Photographic evaluation of skin lesions - only in patients with BHD- associated cutaneous manifestations.																								

3.5 FOLLOW UP EVALUATIONS

After subjects have stopped taking the study medication for any of the reasons listed in Section **3.6.1**, they will be seen at NIH, if feasible, for a safety visit within 4-5 weeks of drug discontinuation. The safety assessments may be performed by a local physician and laboratory if patients unable to return to the NIH Clinical Center at this time.

The following assessments may be completed at the end of treatment +28 days; every effort will be made to complete the following whenever feasible and the patient can comply:

- History and Physical Examination
- Serum Chemistries and CBC/Diff
- HBV DNA, HCV RNA-PCR if indicated

If there are unresolved grade 3 – 4 AEs, patients will be followed either at the NIH clinical center or by their local physician. In the latter case, we will obtain the physician’s record of AEs.

Any scans performed outside of the NIH will also be obtained when possible.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

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

3.6.1 Criteria for removal from protocol therapy

- Completion of protocol therapy.
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in Section **6.2**.
- Investigator discretion
- Positive pregnancy test

3.6.2 Off-Study Criteria

- Completed study follow-up period
- Patient lost to follow-up
- Investigator discretion
- Participant requests to be withdrawn from study
- Death

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3.6.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site

(<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) ncicentralregistration-1@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

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

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study. If indicated, a bisphosphonate or denosumab may be used.

4.1 PERMITTED CONCOMITANT THERAPY

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

Co-administration with strong or moderate inhibitors of CYP3A4 or PgP should be avoided as this may cause increased everolimus concentrations. For a current table of Substrates, Inhibitors and Inducers please access the following website:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall.

Therefore, the following are recommended:

- Co-administration with strong or moderate inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Grapefruit, Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.
- Co-administration of a strong CYP3A4 inducer should be avoided.
- Please refer to Table 4-1 listing relevant inducers and inhibitors of CYP3A and Table 4-2 for a list of relevant substrates, inducers, and inhibitors of PgP.

4.1.2 Everolimus and drugs influencing CYP3A4 enzyme

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent

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elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong or moderate CYP3A4-inhibitors should be avoided. Refer to Table 4-1 for a comprehensive list of inducers and inhibitors of CYP3A4 and Table 4-2 for a list of relevant substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins).

Table 4-1: 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, naftcillin, 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, mibepradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, tipranavir, elvitegravir, Posaconazole ³¹
Moderate inhibitors: aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice (citrus paradisi fruit juice), imatinib, tofisopam, verapamil, amprenavir, fosamprenavir, dronedarone

Table 4-2: Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

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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, mibepradil, milk thistle (silybum marianum), nifedipine, nitrendipine, quercetin, quinidine, ranolazine, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, telmisartan, tipranavir, valsopdar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

4.1.3 Vaccinations

Immunosuppressants may affect the response to vaccination and vaccination during treatment with everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with everolimus. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Tumor Biopsy

Tumor biopsies (renal primary or metastases or fibrofolliculomas) may be obtained from patients who have easily accessible lesions at baseline and at 8 weeks following initiation of therapy. The biopsies are optional and not required for trial participation. Core or excisional biopsy of an easily accessible sentinel lesion (such as cutaneous/subcutaneous lesions, percutaneously accessible hepatic lesions, lymph nodes etc.) may be performed. Biopsies that are to be used solely for research purposes will be obtained only if they can be performed with minimal risk of complications from the procedure and only after the procedure has been explained to the patient and informed consent obtained. Major surgical procedures such as laparotomy or laparoscopic procedures will not be performed solely to obtain biopsies for research purposes. The biopsies will be performed by members of the interventional radiology, dermatology or surgical staff. Ideally, 2-4 cores will be obtained as long as patient safety is not compromised. A portion of the biopsies will be frozen in liquid nitrogen immediately and transferred to the UOB laboratory (Contact for receiving and processing specimen: Robert Worell/ Cathy Vocke, Ph.D. - Tel: 301-496-6353). Prior to freezing and depending on tissue availability, a small portion of the biopsy specimen may be transferred under sterile conditions to the UOB laboratory to be used to establish a tumor cell line.

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In addition, attempts will be made to obtain any available archived tumor tissue on all patients to help evaluate FLCN and PTEN/mTOR status and/or components of relevant pathways.

Samples will be processed for the following planned studies. In the event of limited sample availability, we plan to prioritize studies in the order listed below:

- Analysis of somatic FLCN, PTEN, mTOR and other related mutations such as TSC1/2. This will be accomplished by direct sequencing of these genes.
- Analysis of mTOR activity at baseline and comparative analysis in paired pre- and on-treatment tumors when available

Correlative laboratory studies will be performed by investigators in the Urologic Oncology Branch (under the direction of Drs. Linehan, Srinivasan, Bottaro, Neckers) and/or Genitourinary Malignancies Branch (Jane Trepel's laboratory) and may involve collaboration with other NIH intramural investigators. Studies listed will be performed wherever possible and as permitted or dictated by clinical outcome and/or sample and resource availability.

5.1.2 Collection, Storage, Use and Disposition of Human Specimens

5.1.2.1 Clinical Samples

Blood and urine samples for clinically relevant, non-research hematology, serum chemistry, urinalysis, and skin biopsy tissue will be prepared using standard procedures. Routine clinical analyses will be performed by the NIH Clinical Center central laboratories or NCI Pathology department. Samples will be processed and disposed according to standard laboratory procedure.

5.1.3 Storage and Research Use of Human Specimens

5.1.3.1 Sample Collection and Planned Research Studies

Research samples will be collected with a view to performing a variety of correlative/biomarker studies (as indicated in Section **5.1**).

5.1.3.2 Sample Processing and Storage

Each patient research sample will be assigned a unique patient identifier and relevant sample characteristics (such as timing of sample collection, treatment cycle and day identifiers) will be recorded. The location of all samples will be carefully tracked in the secure UOB database. All stored samples will be coded and no identifying patient information will be placed on sample containers. Stored samples will be kept in freezers / refrigerators or secure containers located in the Urologic Oncology Branch research laboratories or in the laboratories of collaborators.

Timeframe for research studies: Samples will be stored until requested by an authorized researcher(s). All researchers are required to use the samples for research purposes associated with this trial (as per the NCI IRB approved protocol). Subjects will be given the option of consenting to future use of their research samples per the informed consent process with their option declared in the consent document. Samples from those patients who consent to this will be stored permanently. However, these samples will be used only for research studies on active NCI IRB approved protocols covered by a valid informed consent document. Samples will be

destroyed at the completion of the study from those subjects who decline future use of their samples. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent. Any unused samples must be returned to the UOB laboratories as appropriate. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (e.g. broken freezer or lack of dry ice in a shipping container) or if samples are destroyed because a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Any freezer problems, lost samples or other problems associated with samples will be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

Data will be collected prospectively and entered into NCI CCR C3D database. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Grade 1 AEs will be excluded.

6.2 RESPONSE CRITERIA

Restaging will be performed approximately every 12 weeks. Treatment can continue for 52 weeks in the absence of unacceptable toxicity or disease progression.

In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).³² Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

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6.2.1 Definitions

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

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

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.2.2 Disease Parameters

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

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

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target

lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

6.2.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in

accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.³³⁻³⁵ In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.³⁵

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

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

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

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy

in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

6.2.4 Response Criteria

6.2.4.1 Evaluation of Target Lesions

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

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

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

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

6.2.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

6.2.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

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

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

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

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

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

6.2.5 Duration of Response

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

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

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

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 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 web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form except for grade 1 AEs which can be excluded.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections [7.2](#) and [7.3](#).

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the

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pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

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(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 INVESTIGATOR REPORTING: NOVARTIS INSTRUCTIONS FOR RAPID NOTIFICATION OF SERIOUS ADVERSE EVENTS

All serious adverse events must be reported to Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) and reporting will be done via the Investigators or his/her designee.

All events must be reported, by FAX (877-778-9739) to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence. This includes all serious, related, not related, labelled (expected) and unlabelled (unexpected) adverse experiences.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the 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).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

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

7.2.1 Pregnancies

Any pregnancy that occurs during study participation should be reported by the site. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

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

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Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

7.3 NCI-IRB AND NCI CLINICAL DIRECTOR (CD) REPORTING

7.3.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI CD:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

7.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
 - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
 - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
 - All Grade 5 events regardless of attribution;
 - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.3.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.4 DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

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All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

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

8 STATISTICAL CONSIDERATIONS

This trial will follow a two-stage minimax design, where 12 patients will be recruited at the first stage. The trial is designed to distinguish between a 5% vs. 25% response rate. If none of the patients respond to therapy, treatment will be deemed ineffective and recruitment for additional patients will be terminated. Otherwise, an additional 4 patients will be recruited in the second stage, yielding a maximum of 16 patients. Treatment will be considered effective if at least 3 patients respond. This will give an 80% power to declare everolimus effective if the response rate is 25% and a 10% type I error if the response rate is 5%. Under this design, the probability of early termination is 54% and the expected sample size is 13.8 if the response rate is 5%.

Up to 16 evaluable patients will be accrued. To allow for inevaluable patients, accrual ceiling will be set at 18. Anticipated duration of study is 2-3 years based on anticipated accrual of 0-1 patient per month.

9 COLLABORATIVE AGREEMENTS

9.1 AGREEMENT TYPE

This agent for this study, everolimus is being provided to the NIH under a cooperative research and development agreement (CRADA) with Novartis, the manufacturer of the agent.

10 HUMAN SUBJECTS PROTECTIONS

10.1 RATIONALE FOR SUBJECT SELECTION

Patients of all races, genders and ethnic origins will be eligible. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

10.2 PARTICIPATION OF CHILDREN

This protocol will exclude children below 18 years of age since there are no safety data available in this group of patients.

10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become

decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects \geq age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the “NIH Advance Directive for Health Care and Medical Research Participation” form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

10.4.1 Benefits

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or outcome.

10.4.2 Risks

10.4.2.1 Study Agent

The primary risks of participation in this study include the possible occurrence of any of a range of side effects from the study agent everolimus which are listed in the Section **11.1**, the package insert and in the consent document. Frequent monitoring for adverse effects and exclusion of subjects at risk for these adverse effects will help to minimize the risks associated with administration.

10.4.2.2 Optional biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI’s Clinical Center in Bethesda, MD.

Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

Some biopsies may be performed with CT guidance. If that is the case, then this research study involves exposure to radiation from up to 2 CT scans with combined effective dose of 0.29 rem. This is below the guideline of 5.0 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

10.5 RISKS/BENEFITS ANALYSIS

Patients with BHD associated renal tumors typically undergo nephron sparing surgery when one or more tumors reach a size of approximately 3cm, to minimize the risk of metastatic spread. Once metastasis develops, there is no known curative therapy and no established systemic standard of care. Surgery, while safe in most patients, can be associated with morbidity. Furthermore, surgery is not curative and patients are at risk lifelong for the development of new renal tumors. Some patients require repeat surgery and most patients require lifelong

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surveillance. Patients participating in this trial may derive a benefit from the treatment administered. Although the possible toxicities from the proposed therapy may be potentially serious, given the nature of the underlying disease, they are acceptable. For these reasons, the risk/benefit ratio of this protocol is acceptable. This protocol involves greater than minimal risk to patients, but presents the potential for direct benefit to individual subjects.

10.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

Fertile men and women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

For the optional research biopsy, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

10.6.1 Telephone Re-Consent Procedure

Re-consent on this study may be obtained via telephone according to the following procedure: The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

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10.6.2 Informed Consent of Non-English Speaking Subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

11 PHARMACEUTICAL INFORMATION

11.1 EVEROLIMUS

(Please refer to the Package Insert for details)

11.1.1 Source

Everolimus is supplied by Novartis.

11.1.2 Toxicity

Everolimus has been evaluated as a single agent and in combination with other antitumor agents, including cytotoxic chemotherapeutic agents, targeted therapies, antibodies and hormonal agents.

Approximately 25,645 patients (excluding those patients who received marketed Afinitor®/Votubia®) have been treated with everolimus as of 30-Sep-2012: of which 13,229 patients in Novartis-sponsored clinical trials; 2,624 patients in the single patient use IND program; and 9,792 in investigator-sponsored studies. In addition, healthy volunteer subjects and hepatically impaired non-oncology subjects have participated in the clinical pharmacology studies described in the Investigator's Brochure.

11.1.3 Formulation and preparation

Everolimus is formulated as tablets for oral administration of 2.5mg, 5mg, and 10mg 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. Refer to label for expiration date and storage conditions.

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

11.1.4 Stability and Storage

The storage of all formulations is supported by ongoing stability studies. Refer to label for expiration date and storage conditions.

11.1.5 Administration procedures

Everolimus should be administered 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 until the tablet(s) is fully disintegrated (approximately 7 minutes), 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.

11.1.6 Incompatibilities

Refer to the concomitant medications in Section 4 and the package insert for details.

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13 APPENDICES**13.1 APPENDIX A: PERFORMANCE STATUS CRITERIA**

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	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.

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13.2 APPENDIX B: EVEROLIMUS PILL AND SIDE EFFECTS DIARY

Today's date _____ Cycle _____ Week _____ Dose _____

Patient Name _____ Patient Study ID _____
(initials acceptable)

Date	Day #	Time Taken	SIDE EFFECTS/COMMENTS	Init
	#1			
	#2			
	# 3			
	# 4			
	# 5			
	# 6			
	# 7			

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Patient's planned daily dose _____
3. Total number of pills taken this week _____

Physician/Nurse/Data Manager's Signature _____

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13.3 APPENDIX C: PATIENT INSTRUCTIONS FOR EVEROLIMUS THERAPY

You are participating in a study of Everolimus and its effectiveness in the treatment of kidney cancer. It is important that you take your medication as instructed. If you are unable to take the medication as instructed, you should contact the Study Team as soon as possible. Please keep in mind the following:

- You should take your medication once/ day, at approximately the same time every day. You should take the medication with a full glass of water. You may take the medication with or without food, whichever you choose, but should take it that way consistently. Record the date and time you have taken the medication on your diary.

If you should vomit your medication after taking it, do not take the medication again.

- Record any side effects you experience on your diary. Bring your Pill and Side Effect diaries, your remaining medication, and empty pill vials with you to each appointment.
- You cannot eat grapefruit, Seville oranges, or star fruit, or drink their juices while on this study.
- Your medication may decrease the effectiveness of your immune system. Wash your hands frequently, and avoid others with cold symptoms. If you develop a cough, fever, painful urination, sore throat, runny nose, or any symptom that does not feel right, call your study team. DO NOT RECEIVE VACCINES while on study until you check with your study team first! You cannot have close contact with individuals who have received live vaccines such as measles, mumps, rubella, varicella, typhoid, oral polio, BCG, or yellow fever for 4 weeks post vaccination.
- Your medication may also affect your lungs. If you develop shortness of breath, at rest or on exertion, chest pain, or cough, call your study team as soon as possible.
- A common side effect of your medication is sores in your mouth. Perform frequent oral hygiene, but avoid mouthwashes with alcohol. If you develop a mouth sore, rinse frequently with warm saline mouth rinses, or the mouth rinses provided by your study team. Eat soft, bland food. If you are having difficulty eating or drinking, call your study team immediately.
- Avoid sun exposure, and always wear sunscreen when outdoors (> SPF 30).
- Do not drink alcohol (including beer and wine) unless approved by the study team.
- If you should need dental work or surgery, notify your team immediately.
- You will be given medication at the beginning of the trial to be used only as needed. If you need any of these medications, follow the directions on the label, and record that you have taken the medication in your diary. If the symptoms persist even after taking the medication, call your study team. These medications are: 1.Ondansetron (Nausea); 2.Loperamide (Diarrhea); 3.Colace (Constipation); 4. Lidobenalox Oral Solution (Mouth Sores).

Please call your study team with ANY questions or change in your condition.

**Martha Ninos RN (Study Coordinator)
Julia Friend PA-C**

240-760-6248 (Mon-Fri: 8-4PM) *
301-240-271-8121 (Mon-Fri: 8-4PM) *****

***** Evenings, weekends, and emergencies call Hospital paging @ 301-496-1211 and ask to speak to the Urology Fellow On Call**