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## SWOG

EVEREST: EVERolimus for Renal Cancer Ensuing Surgical Therapy, A Phase III Study

NCT #01120249

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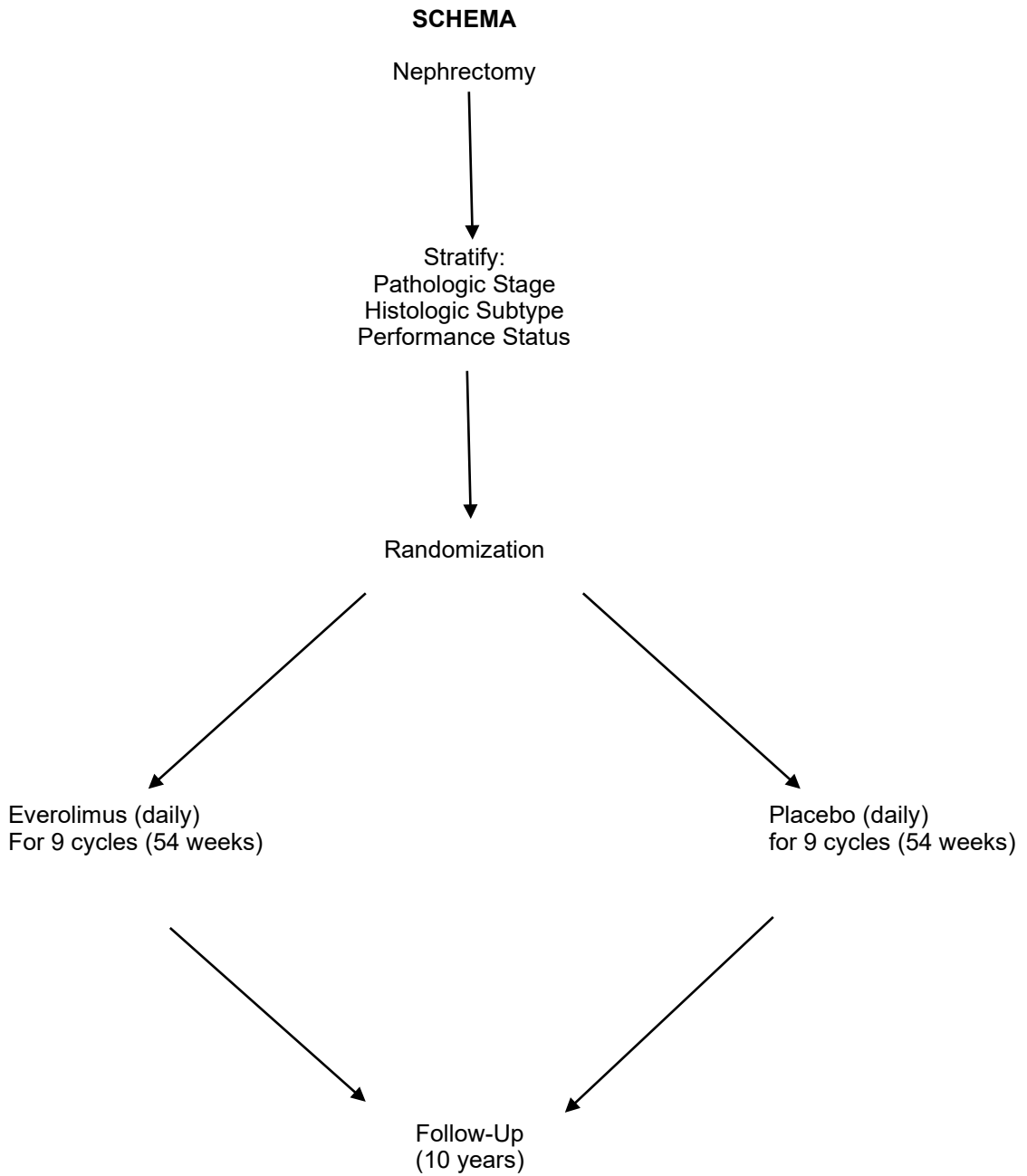
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**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103</p> <p>Fax: 215-569-0206</p> <p>Email: CTSURegulatory@ctsu.coccg.org</p> <p>For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at <a href="https://www.ctsu.org/OPEN_SYSTEM/">https://www.ctsu.org/OPEN_SYSTEM/</a> or <a href="https://OPEN.ctsu.org">https://OPEN.ctsu.org</a>.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>.</p>	<p><u>Online Data Submission:</u> Institutions participating through the CTSU are required to submit and amend their data electronically via Online Data Submission. Access the SWOG Workbench using your CTSU User ID and password at the following url:  <a href="https://crawb.crab.org/TXWB/ctsulogon.aspx">https://crawb.crab.org/TXWB/ctsulogon.aspx</a></p> <p><u>Exceptions:</u> Data items that are not available for online submission (operative and pathology reports, patient completed forms, scan reports, etc.) may be submitted by fax at 800-892-4007.</p> <p>Do not submit data forms to CTSU Data Operations.</p> <p>Do not copy the CTSU on data submission.</p>
<p>The most current version of the <b>study protocol and all supporting documents</b> must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <a href="https://www.ctsu.org">https://www.ctsu.org</a>. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.</p>		
<p><b>For patient eligibility questions</b> contact the SWOG Data Operations Center by phone or email:</p> <p>Phone: 206/652-2267 E-mail: <a href="mailto:guquestion@crab.org">guquestion@crab.org</a></p>		
<p><b>For treatment or toxicity related questions</b> contact the Study PI of the Coordinating Group (Dr. Christopher Ryan at 503/494-8487).</p>		
<p><b>For questions unrelated to patient eligibility, treatment, or data submission</b> contact the CTSU Help Desk by phone or e-mail:</p> <p>CTSU General Information Line: 888-823-5923 E-mail: <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a></p> <p>All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><b>For detailed information on the regulatory and monitoring procedures for CTSU sites</b> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website:</p> <p><a href="https://www.ctsu.org">https://www.ctsu.org</a> &gt; education and resources tab &gt; CTSU Operations Information &gt; CTSU Regulatory and Monitoring Policy</p>		
<p><b>The CTSU website is located at</b> <a href="https://www.ctsu.org">https://www.ctsu.org</a></p>		





NOTE: Procedure for optional unblinding of treatment at recurrence outlined in [Section 7.5](#).

## 1.0 OBJECTIVES

### 1.1 Primary Objective

The primary objective of this study is to compare recurrence-free survival in renal carcinoma patients randomly assigned to 54 weeks of everolimus versus 54 weeks of placebo after nephrectomy or partial nephrectomy.

### 1.2 Secondary Objectives

- a. To compare overall survival in those patients randomized to everolimus versus those randomized to placebo.
- b. To compare qualitative and quantitative toxicity between the two study arms.

### 1.3 Translational Medicine Objectives

- a. To bank tissue and biologic specimens for future study of molecular biomarkers relevant to the AKT/mTOR and other pathways implicated in the pathogenesis of renal carcinoma and to investigate their potential predictive and prognostic value.
- b. To bank blood specimens for the future study of the relationship between steady state trough levels of everolimus and relevant side effects (lymphopenia, infection, hyperglycemia, hypercholesterolemia, hypertriglyceridemia) in patients treated on this study with everolimus.

## 2.0 BACKGROUND

Nearly 58,000 patients are expected to be diagnosed with kidney cancer in the United States in 2009. (1) Despite significant improvements made over the last several years in treatment of advanced kidney cancer, 13,000 patients are expected to die from their disease in 2009. Many of these patients originally present with localized disease and are treated with surgical resection with curative intent. However, up to one-third of patients with fully resected, localized disease will develop either a local or distant recurrence; the majority of whom will succumb to distant metastases. (2,3) Despite this significant risk, current standard treatment after resection in these patients is surveillance. Multiple studies investigating interferon or interleukin-2 in the adjuvant setting have failed to demonstrate any benefit over observation alone. (4,5,6,7) Studies investigating autologous tumor vaccines have shown equivocal results. (8,9) Such first-generation adjuvant studies predated VEGF- and mTOR-directed therapies which have now been established in the treatment of advanced disease based on improved progression-free- and overall-survival. (10,11,12,13,14,15)

The Eastern Cooperative Oncology Group **E2805** study (ASSURE) is a second-generation adjuvant study investigating the potential role of the multi-kinase inhibitors sorafenib and sunitinib as adjuvant therapy in the post-operative setting for patients with fully resected localized disease. ASSURE is a randomized Phase III study of one year of sunitinib versus one year of sorafenib versus one year of placebo in patients with intermediate to high-risk M0 renal carcinoma beginning within 12 weeks of nephrectomy. (16) This study completed accrual September 1, 2010. It is likely that results will not be available for several years after study closure. Until the results of ASSURE are known, surveillance will remain as standard treatment for such patients. Several additional industry-sponsored, international trials investigating the utility of adjuvant VEGF-R tyrosine kinase inhibitors are currently enrolling, including the SORCE trial (sorafenib), S-TRAC trial (sunitinib), NCT 00492258, NCT 00375674, and NCT 01235962.

ASSURE was designed to study the adjuvant activity of sunitinib and sorafenib, the first two agents to receive FDA approval for advanced renal carcinoma in the post-immunotherapy era, both of



which are VEGF-R tyrosine kinase inhibitors. Inhibitors of mTOR have since emerged as treatment options for advanced renal carcinoma. mTOR is a serine/threonine kinase that recognizes stress signals via the PI3K-AKT pathway and phosphorylates p70 ribosomal S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E binding protein 1 (4EBP1). Its role in progression of renal carcinoma may be due to its downstream regulation of hypoxia-inducible factor 1- $\alpha$ . (17) Recent Phase III studies have established mTOR inhibition as a clinically relevant treatment strategy for advanced renal carcinoma. In a Phase II trial, temsirolimus, a pro-drug of rapamycin, was shown to improve progression-free and overall-survival in modified Memorial Sloan-Kettering Cancer Center (MSKCC) criteria poor-risk, advanced renal carcinoma patients, and received FDA approval for treatment of the disease. (18,19) Everolimus is an orally-administered derivative of rapamycin that was studied in a placebo-controlled Phase III study in patients with advanced renal carcinoma who had received prior therapy with sorafenib, sunitinib, or both. In this study, everolimus improved progression-free survival compared with placebo (hazard ratio 0.30, 95% CI 0.22–0.40,  $p < 0.0001$ ) and has been FDA-approved for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. (20)

### Everolimus

Everolimus is an orally bioavailable macrolide derivative of rapamycin that targets the activity of mTOR kinase and demonstrates potent antiproliferative effects against a variety of tumor types in the pre-clinical setting. (21) Everolimus exerts its activity through high affinity interaction with an intracellular receptor protein, the immunophilin FKBP12. The FKBP12/everolimus complex subsequently interacts with the mTOR protein kinase, inhibiting downstream signaling events involved in regulation of the G1 to S-phase transition. The antitumor effect of everolimus may be due to direct inhibition of tumor cell growth and indirectly by inhibiting angiogenesis. The observation of in vivo sensitivity of xenografts comprised of cells demonstrating resistance to everolimus in vitro attributes to the drugs potential to act on the vascular component of the supporting peritumoral stroma. The antiangiogenic property of everolimus confirmed through experiments demonstrating the effect of everolimus in countering VEGF-induced proliferation of human umbilical endothelial cells (HUVEC) in vitro, VEGF-driven angiogenesis in a chamber implant murine model and neovascularization in a murine orthotopic melanoma model.

### Clinical Development

Everolimus has been extensively investigated as an immunosuppressant in solid organ transplantation and is approved in renal and cardiac transplantation in many countries. Everolimus has been in development for patients with various hematologic and nonhematologic malignancies both as a single agent or in combination with other antitumor agents. Diseases under study included renal cell carcinoma, breast cancer, carcinoid neuroendocrine tumors, pancreatic islet cell tumors (pNET), hematologic malignancies including chronic myelogenous leukemia (CML), non-Hodgkin's and mantle cell lymphoma, hepatocellular, gastric, colorectal, gastrointestinal stromal tumors (GIST), prostate and others.

Phase I studies of cancer patients with single-agent everolimus have been conducted with both weekly and daily regimens. Dose-limiting toxicities included stomatitis, fatigue, hyperglycemia, and neutropenia. (22,23)

A Phase III, randomized, double blind, placebo controlled study in patients with mRCC who progressed on VEGF-R tyrosine kinase inhibitors demonstrated that everolimus administered daily at an oral dose of 10 mg prolonged median progression free survival from 1.87 months for patients receiving placebo to 4.9 months for everolimus treated patients (hazard ratio 0.33, 95% CI 0.25-0.43,  $p < 0.0001$ ). (24,25)

Everolimus 5 mg and 10 mg tablets were recently approved under the trade name Afinitor® for patients with advanced renal cell carcinoma (RCC) after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide.





The most common treatment-related adverse effects observed in the renal carcinoma study included stomatitis (40%), rash (40%), fatigue (20%), asthenia (18%), diarrhea (17%), anorexia (16%), and nausea (15%). The most common laboratory abnormalities include anemia (91%), hypercholesterolemia (76%), hypertriglyceridemia (71%), hyperglycemia (50%), increased creatinine (46%), and lymphopenia. (42%). (26)

#### Study Rationale

Given that mTOR inhibition has been shown to improve progression-free survival in two different patient populations of advanced renal carcinoma, it is warranted to study an mTOR inhibitor in the adjuvant setting. Everolimus has the advantage of oral dosing, making it potentially more suitable for adjuvant administration, and has been chosen for this study. The dosing will be 10 mg orally once daily which is the dosing schedule used in the Phase III trial and was the maximum daily dose evaluated in Phase I cancer trials. (27,28,29) The control arm will be placebo with a randomized double-blind design, justified by the fact that surveillance is the current standard treatment in this disease setting. We hypothesize that one year of adjuvant treatment with everolimus will improve recurrence-free survival without addition of excessive toxicity.

Accrual to the ASSURE trial was quicker than anticipated with a projected accrual rate of 480 patients per year. However, a high treatment discontinuation rate was noted with approximately 25% of patients on the active arms discontinuing treatment within three months due to adverse events or patient refusal. ASSURE was amended to lower the starting doses of sorafenib and sunitinib in an attempt to ameliorate these effects and to increase the sample size to account for the high dropout rate. Given that everolimus has a different side effect profile than sunitinib or sorafenib, it is quite possible that this agent may be more tolerable in the adjuvant setting and result in better patient adherence. As an example, hand foot syndrome is not a common side effect of mTOR inhibitor therapy, and this particular toxicity has been cited as one of the potential early-onset VEGF-TKI toxicities that have influenced the ASSURE dropout rate. (30)

ASSURE employs the UCLA Integrated Staging System (UISS) in determining risk grouping. (31) Intermediate-risk, high-risk, and node-positive patients were eligible for ASSURE, based on an analysis of the UCLA database that demonstrated a five year recurrence free rate of 61.8% in the intermediate risk group, 41.9% in the high risk group, and 36% in the node-positive group. (32) Although it was expected that 69% of accrued subjects would be intermediate risk and 31% would have high-risk or node positive disease (“very high-risk”), actual accrual numbers reveal that a full 50% of accrued patients are very-high risk. (33) We therefore expect a significant proportion of very-high risk patients to be enrolled in this trial, a population in whom mTOR inhibition may theoretically be most relevant given its proven effectiveness in metastatic poor prognosis patients. (34) If that proportion of very-high risk patients is not met, closure of lower risk strata will occur to ensure adequate representation. Similarly, given the potential particular activity of mTOR inhibition in non-clear cell histology renal carcinoma, accrual of non-clear cell subjects will be ensured by closure of the clear-cell strata if adequate representation is not achieved. (35)

#### Translational Medicine

##### Predictive and Prognostic Value of AKT/mTOR Pathway Status in Intermediate and High-Risk, Localized Renal Carcinoma

In order to investigate molecular biomarkers relevant to AKT/mTOR pathway inhibition in this trial, relevant translational studies are planned. The overall **hypothesis** is that patients with RCC tumors characterized by AKT/mTOR pathway activation will benefit from mTOR-targeted therapy. In light of the paucity of information regarding the role of AKT/mTOR activation in post-nephrectomy tumor recurrence and survival, it is critical to distinguish between the prognostic and/or predictive roles of these biomarkers. In the context of this Phase III trial, the following aims are proposed: 1) To define the status (activation, expression and functional) of factors involved in AKT/mTOR signaling in RCC tumor specimens, including AKT, mTOR, S6K, 4EBP1, HIF $\alpha$ , vHL, PTEN and other pathway-specific factors. 2) To perform exploratory microarray analysis in tumor tissue to identify genes and pathways prognostic for recurrence and/or predictive of response to everolimus. Pathways to be analyzed will include but not be limited to PI3K-AKT-mTOR, HIF-1 $\alpha$  protein translation and VEGFR-PDGFR (using Ingenuity Pathway



Analysis). Additionally, levels of tumor-associated plasma proteins from serial draws will be examined using multiplex analysis. 3) To correlate molecular biomarkers with patient outcome, including recurrence-free survival and overall survival, and to identify specific cohorts of patients, categorized by molecular phenotype, who benefit from everolimus therapy.

The following specimens will be collected for the above studies (further described in [Section 15.0](#)): 1) Tissue specimen: a paraffin embedded nephrectomy block will be collected from all consenting patients; 2) blood specimens: (plasma and buffy coats) for correlative studies will be collected after registration, but prior to treatment; at the beginning of Cycles 2 and 3; at the end of therapy (54 weeks); and at the time of recurrence.

#### Pharmacodynamic Evaluation of Everolimus in Adjuvant Renal Carcinoma Subjects

Everolimus was originally developed for its immunosuppressant properties in the prevention of rejection after solid-organ transplantation. Chronic daily dosing of an mTOR inhibitor has not been studied in an adjuvant cancer population, and potential adverse effects of longer-term administration of everolimus need to be carefully assessed. While this trial will evaluate one year of adjuvant therapy, it is possible that longer dosing duration may eventually prove advantageous, and understanding and predicting for chronic toxicity is important in this population. We will therefore study adverse effects of everolimus in this study population and determine a relationship with steady-state trough levels of the drug.

The published literature on steady-state pharmacokinetics and chronic toxicity has largely been in the post-transplant setting in which everolimus has been co-administered with other immunosuppressant drugs as part of triple-therapy rejection prophylaxis. (36,37) The applicability of this toxicity data to the adjuvant renal carcinoma population is clouded by the potential contribution of co-administered immunosuppressant drugs and other factors peculiar to post-transplant setting. Since the adjuvant renal carcinoma setting represents a population with curative potential, mTOR inhibitor side effects with potential long-term implications are of concern, including hyperlipidemia and immunosuppression, which may be a particular issue with the daily dosing regimen studied in cancer. (38)

In renal transplantation patients, steady-state minimum concentrations were well correlated with AUC (correlation coefficient [r value] = 0.88). (39) A relationship was seen between AUC and thrombocytopenia ( $p=0.03$ ), and there was a positive trend between AUC and both hypercholesterolemia and hypertriglyceridemia. These results suggest that monitoring  $C_{min}$  may serve as a good marker for overall everolimus exposure. (40) In the post-transplantation setting, trough levels are recommended to be in the desired range of 3 to 8 ng/mL to optimize efficacy and decrease the incidence of adverse reactions, although it has been suggested that everolimus use with levels of up to 15 ng/mL is manageable. (41,42) In Phase I studies in advanced cancer patients using 10 mg daily dosing, trough levels exceeded the recommended range for the transplant population. (43,44)

In order to investigate the relationship between steady-state trough concentrations of everolimus in adjuvant renal cancer patients and drug toxicity, we will collect specimens to study the incidence of lymphopenia, infection, thrombocytopenia, hyperglycemia, hypercholesterolemia, hypertriglyceridemia, stomatitis, creatinine elevation, and non-infectious pneumonitis as pharmacodynamic markers of everolimus exposure. Blood sampling for pre-dose trough levels of everolimus will be obtained after registration, but prior to treatment; at the beginning of Cycles 2 and 3; and at the time the patient is removed from protocol treatment. Everolimus whole-blood concentrations will be determined via high-performance liquid chromatography/mass spectroscopy assay. Relationships between everolimus steady-state  $C_{min}$  and the incidence of specific toxicities will be explored.

Trough levels of everolimus in post-nephrectomy renal carcinoma patients will correlate with toxicity and yield an upper threshold level that can be used in developing a therapeutic range for everolimus in the adjuvant population.



Inclusion of Women and Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. Both men and women of all races and ethnic groups are eligible for this study.

<b>Ethnic Category</b>	<b>Females</b>	<b>Males</b>	<b>Total</b>
Hispanic or Latino	55	89	144
Not Hispanic or Latino	436	957	1393
<b>Total Ethnic</b>	491	1046	1537
<b>Racial Category</b>			
American Indian or Alaskan Native	1	4	5
Asian	10	42	52
Black or African American	29	42	71
Native Hawaiian or other Pacific Islander	0	0	0
White	451	958	1409
<b>Racial Category: Total of all Subjects</b>	491	1046	1537

### 3.0 DRUG INFORMATION

Investigator's Brochure

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, everolimus is investigational and is being provided under an IND held by SWOG. For IND's filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

#### 3.1 Everolimus (RAD001, Afinitor®, Zortress®) (NSC- 733504) (IND-75,093)

##### a. PHARMACOLOGY

Mechanism of Action: Everolimus binds to the cytosolic immunophyllin FKBP12; both agents inhibit growth factor-driven cell proliferation, including that of T-cells and vascular smooth muscle cells. The everolimus and FKBP12 complex selectively inhibits mTOR (mammalian target of rapamycin), an intracellular protein kinase implicated in the control of cellular proliferation of neoplastic cells, specifically in the progression of cells from G1 to S phase. Everolimus also reduces angiogenesis by inhibiting VEGF and HIF-1 expression.

##### b. PHARMACOKINETICS

1. Absorption: Everolimus levels peak in 1-3 hours after oral administration. There is rapid but moderate absorption.
2. Distribution: Everolimus is about 74% protein bound in healthy subjects and patients with moderate hepatic impairment.



3. **Metabolism:** Everolimus is extensively metabolized by CYP3A4 and forms 6 weak metabolites. It is also a P-glycoprotein substrate.
4. **Elimination:** Everolimus is extensively eliminated via the bile. The elimination half-life of everolimus is about 30 hours and is prolonged in patients with hepatic impairment. Everolimus is primarily excreted through the feces.

c. ADVERSE EFFECTS

1. The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf) for further clarification. *Frequency is provided based on 3033 patients.* Below is the CAEPR for Everolimus (RAD-001).

**NOTE:** Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 10, 2017<sup>1</sup>

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>			
Anemia			<b><i>Anemia (Gr 2)</i></b>
<b>GASTROINTESTINAL DISORDERS</b>			
	Abdominal pain		
	Constipation		
Diarrhea <sup>2</sup>			<b><i>Diarrhea<sup>2</sup> (Gr 2)</i></b>
Mucositis oral <sup>3</sup>			<b><i>Mucositis oral<sup>3</sup> (Gr 2)</i></b>
	Nausea		<b><i>Nausea (Gr 2)</i></b>
	Vomiting		<b><i>Vomiting (Gr 2)</i></b>
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>			
	Edema limbs		<b><i>Edema limbs (Gr 2)</i></b>
Fatigue			<b><i>Fatigue (Gr 2)</i></b>
	Fever		<b><i>Fever (Gr 2)</i></b>
<b>INFECTIONS AND INFESTATIONS</b>			
	Infection <sup>4</sup>		<b><i>Infection<sup>4</sup> (Gr 2)</i></b>



<b>Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]</b>			<b>Specific Protocol Exceptions to Expedited Reporting (SPEER)</b>
<b>Likely (&gt;20%)</b>	<b>Less Likely (&lt;=20%)</b>	<b>Rare but Serious (&lt;3%)</b>	
<b>INJURY, POISONING AND PROCEDURAL COMPLICATIONS</b>			
		Wound complication <sup>5</sup>	
<b>INVESTIGATIONS</b>			
	Alanine aminotransferase increased		<b>Alanine aminotransferase increased (Gr 2)</b>
	Alkaline phosphatase increased		<b>Alkaline phosphatase increased (Gr 2)</b>
	Aspartate aminotransferase increased		<b>Aspartate aminotransferase increased (Gr 2)</b>
	Cholesterol high		<b>Cholesterol high (Gr 2)</b>
	Creatinine increased		<b>Creatinine increased (Gr 2)</b>
	Lymphocyte count decreased		<b>Lymphocyte count decreased (Gr 2)</b>
	Neutrophil count decreased		<b>Neutrophil count decreased (Gr 2)</b>
	Platelet count decreased		<b>Platelet count decreased (Gr 2)</b>
	Weight loss		
	White blood cell decreased		<b>White blood cell decreased (Gr 2)</b>
<b>METABOLISM AND NUTRITION DISORDERS</b>			
	Anorexia		<b>Anorexia (Gr 2)</b>
	Hyperglycemia <sup>6</sup>		<b>Hyperglycemia<sup>6</sup> (Gr 2)</b>
	Hypertriglyceridemia		<b>Hypertriglyceridemia (Gr 2)</b>
	Hypophosphatemia		<b>Hypophosphatemia (Gr 2)</b>
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>			
	Arthralgia		
	Back pain		
	Pain in extremity		
<b>NERVOUS SYSTEM DISORDERS</b>			
	Dysgeusia		
	Headache		<b>Headache (Gr 2)</b>
<b>RENAL AND URINARY DISORDERS</b>			
		Acute kidney injury	
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>			
	Cough		<b>Cough (Gr 2)</b>

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
	Dyspnea		<i>Dyspnea (Gr 2)</i>
	Epistaxis		<i>Epistaxis (Gr 2)</i>
	Pneumonitis <sup>7</sup>		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
Rash maculo-papular			<i>Rash maculo-papular (Gr 2)</i>
		Skin and subcutaneous tissue disorders - Other (angioedema) <sup>8</sup>	

<sup>1</sup> This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

<sup>2</sup> Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

<sup>3</sup> Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

<sup>4</sup> Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

<sup>5</sup> Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.

<sup>6</sup> Hyperglycemia may result in either exacerbation of or development of new onset diabetes mellitus.

<sup>7</sup> Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.

<sup>8</sup> Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

<sup>9</sup> Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

**Adverse events reported on Everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Everolimus (RAD-001) caused the adverse event:**



**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Blood and lymphatic system disorders - Other (thrombotic microangiopathy)

**CARDIAC DISORDERS** - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia

**ENDOCRINE DISORDERS** - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Endocrine disorders - Other (low testosterone); Hypothyroidism

**EYE DISORDERS** - Blurred vision; Conjunctivitis; Keratitis

**GASTROINTESTINAL DISORDERS** - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache

**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Edema trunk; Flu like symptoms; Irritability; Non-cardiac chest pain; Pain

**HEPATOBIILIARY DISORDERS** - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)

**IMMUNE SYSTEM DISORDERS** - Allergic reaction

**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Investigations - Other (bicarbonate decreased); Investigations - Other (increased lactate dehydrogenase); Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia)

**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia); Metabolism and nutrition disorders - Other (hyperlipidemia)

**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia

**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)

**NERVOUS SYSTEM DISORDERS** - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia

**PSYCHIATRIC DISORDERS** - Agitation; Anxiety<sup>9</sup>; Delirium; Depression; Insomnia; Mania

**RENAL AND URINARY DISORDERS** - Hematuria; Proteinuria; Urinary frequency

**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage

**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea); Sore throat; Voice alteration

**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration



**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage)

**Note:** Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy category D. It is not known if everolimus is excreted in human milk.

Drug Interactions: Everolimus is a substrate of cytochrome P450 3A4 (CYP3A4) and also a substrate and moderate inhibitor of the multidrug efflux pump P-glycoprotein (PgP). *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Due to the extensive number of everolimus drug interactions, a complete patient medication list, including everolimus, should be screened prior to initiation of everolimus (as indicated in [Section 7.3](#) and [Appendix 18.3](#)).

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

3. Hepatic Impairment: Dosage adjustment of everolimus is recommended in moderate hepatic impairment (Child-Pugh class B). Contact the Study Chair for guidance. Use of everolimus is not recommended in severe hepatic impairment (Child-Pugh class C).

d. **DOSING & ADMINISTRATION**

1. Dosing – See Treatment Plan (see [Section 7.2](#))
2. Everolimus (or matching placebo) should be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets should be swallowed whole with a glass of water. Grapefruit or citrus juices should be avoided. The tablets must not be chewed or crushed. If unable to swallow whole tablet, may disperse tablet completely in 30 mL water and drink immediately; rinse container with additional 30 mL water and swallow.

e. **STORAGE & STABILITY**

The intact blister packs should be stored at controlled room temperature (15°-30°C) and protected from light. Current stability data permit shelf life of 24 months for 5 mg tablet variant based on solid dispersion dried by paddle dryer and 36 months for 5 mg tablet variant based on solid dispersion dried by evaporation/drying oven if stored below 30°C in the original double sided aluminum blister and protected from light and moisture.

f. **HOW SUPPLIED**

1. Everolimus or matching placebo will be supplied as tablets blister-packed under aluminum foil in units of 10 tablets. Blisters should be opened only immediately prior to ingestion as the drug is both hygroscopic and light-sensitive.





Everolimus or matching placebo 5 mg tablets are white to slightly yellow, elongated tablets with a beveled edge and no score, engraved with “5” on one side and “NVR” on the other.

Everolimus is commercially available, however it is considered investigational for this study. Everolimus 5 mg tablets and placebo to match everolimus 5 mg tablets will be supplied by Novartis Pharmaceuticals Corporation and will be distributed by the Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC). Each participating Institution must have a Pharmacy ID Number, in addition to their Institution Number, before randomization of subjects can begin. SWOG institutions already have a pharmacy associated with them, so they do not need to report a Pharmacy ID number since that information is already linked in the SWOG database. However, Institutions registering via CTSU must be assigned a pharmacy ID number by the PCC. With the initial and each subsequent randomization, the Institution registering via CTSU will be required to provide their Institution’s Pharmacy ID Number. No randomizations can be completed without a Pharmacy ID Number. For CTSU Participating Institutions, each Institution must call the PCC at (505) 248-3203 to register their Institution with the PCC and receive a Pharmacy ID Number. This registration by CTSU Participating Institutions with the PCC must be completed at least 1 working day prior to the randomization of the first subject at the site or randomization of the first subject will have to be postponed. When calling the PCC, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct PCC staff, the caller should indicate the “SWOG protocol “S0931”, “EVEREST”, or “P261” (the PCC internal number for the study). To register an Institution, the PCC will require:

- the name of the receiving individual,
- complete street address, and phone number,
- e-mail address of the receiving individual.

Everolimus or matching placebo will be packaged by the PCC and supplied to the Institutions in kits of 10 blister cards, with each kit containing sufficient drug for one cycle of treatment. No supply of unassigned everolimus or matching placebo will be maintained at the institutions. Rather everolimus or matching placebo will be supplied to the site in a “just in time” manner. **Upon notification of a randomization by the SWOG Statistical Center, the PCC will ship the first patient-specific kit to an Institution to arrive within four working days.** Each kit will be labeled specifically for an individual subject with the subject’s SWOG Patient Number.

Subsequent patient-specific kits will automatically be shipped to the Institution approximately mid-cycle of Cycles 1-8. The blister card and kits labels will be permanently attached. The site will write down the kit numbers on the Drug Accountability Record Form when the kit is dispensed.

If a subject requires a replacement kit (Emergency Kit) for lost (etc.) medication, an Emergency Kit should be supplied by calling the PCC at 505/248-3203.

Prior to dispensing the next kit of study medication, or at the study visit at the end of everolimus or placebo treatment, the old blister cards and any



unused tablets are to be collected from the subjects and quantity remaining logged on to the Drug Accountability Records. Any unused, partially used, or expired study drug remaining when a subject goes off treatment should be destroyed on-site in accordance with local institutional policy. In the event that a site does not have documented destruction procedures in place, call PCC at (505/248-3203 for instructions on how to return leftover study drug.

2. Drug Handling and Accountability
  - a. Drug accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and destruction of all study drugs received from the distributor using the NCI Oral Drug Accountability Record Form (NCI Oral DARF), available at <http://ctep.cancer.gov>. A separate record must be maintained for each patient on this protocol.
  - b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI Oral DARF.
3. Drug Return and/or Disposition Instruction
  - a. Drug Returns: All unused drug, unopened and unused blister cards remaining when a subject goes off treatment, and expired blister cards should be destroyed on-site in accordance with institutional policy. Partially used blister cards with remaining tablets should be documented in the patient-specific accountability record (i.e., logged in as "# of tablets returned") and destroyed on-site in accordance with institutional policy.
  - b. Drug Transfers: Blister cards **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g. a patient moves from one participating institution to another participating institution) must be approved **in advance** by calling the PCC at (505) 248-3203.

Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PCC at (505) 248-3203.

#### 4.0 STAGING CRITERIA

##### DEFINITION OF TNM (AJCC Seventh Edition, 2010)

##### Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney



T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's Fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's Fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's Fascia (including contiguous extension into the ipsilateral adrenal gland). NOTE: Non-contiguous adrenal lesion is considered M1 disease and not eligible for protocol participation.

### **Regional Lymph Nodes (N)**

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)

### **Distant Metastasis (M)**

M0	No distant metastasis
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### **HISTOLOGIC GRADE (G)**

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

### **PATHOLOGIC STAGE**

#### **Intermediate High-Risk Group**

pT1b	G3-4, N0 (or pNX where clinically N0), M0
pT2a-b	G1-2, N0 (or pNX where clinically N0), M0
pT2 a-b	G3-4, N0 (or pNX where clinically N0), M0
pT3a	G1-2, N0 (or pNX where clinically N0), M0

Microvascular invasion of the renal vein of pT1a-pT3a (as long as pT3a is Grade 1-2) N0 (or pNX where clinically N0) M0

#### **Very High Risk Group**

pT3a	G3-4, N0 (or pNX where clinically N0), M0
pT3b-c	G any, N0 (or pNX where clinically N0), M0
pT4	G any, N0 (or pNX where clinically N0), M0
pT any	G any, N+ (fully resected), M0

Microvascular invasion of the renal vein with above other characteristics

## **5.0 ELIGIBILITY CRITERIA**

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0931** Prestudy Form and submit to the Data



Operations Center in Seattle (see [Section 14.0](#)). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at [guquestion@crab.org](mailto:guquestion@crab.org) or 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 42, or 84 falls on a weekend or holiday, the limit may be extended to the next working day.**

#### 5.1 Disease Related Criteria

- a. Patients must have histologically or cytologically confirmed renal cell carcinoma (clear cell or non-clear cell allowed, but collecting duct or medullary carcinomas excluded). Patients must be considered pathologically either Intermediate High Risk or Very High Risk as defined in [Section 4.0](#). Patients must not have a history of distant metastases. Patients with microvascular invasion of the renal vein of any grade or stage (as long as M0) are also eligible.
- b. Patients must have undergone a full surgical resection (radical nephrectomy or partial nephrectomy), including removal of all clinically positive nodes. Surgical margins must be negative. Patients with positive renal vein margins are eligible unless there is invasion of the renal vein **wall** at the margin (provided no other margins are positive). Patients must plan to start study drug within 84 days after the date of full surgical resection. Patients must have recovered from any surgical related complications.
- c. Patients with bilateral renal tumors are eligible provided both tumors have undergone full surgical resection and at least one of the tumors meets all eligibility criteria in Sections 5.1a-b. Patients must plan to start study drug within 84 days after the date of the resection of the first tumor.
- d. Patients must not have any evidence of residual or metastatic renal cell cancer on CT scan of the chest, abdomen, and pelvis, all with oral and IV contrast after nephrectomy and within a maximum of 28 days prior to registration. An MRI scan of the abdomen/pelvis with gadolinium and a non-contrast CT of the chest is an acceptable imaging alternative. Non-contrast CT of the chest/abdomen/pelvis should only be performed if, in the opinion of the investigator, it is in the best medical interest of the patient to not receive IV contrast of any form. NOTE: PET/CT is not an acceptable imaging alternative. Patients who display subcentimeter pulmonary nodules (by CT scan) that are non-specific and considered unlikely to represent metastatic disease by the treating investigator will be considered eligible.

#### 5.2 Prior Therapy Criteria

- a. Patients must not have received any prior anti-cancer therapy (except for radical or partial nephrectomy noted above) for renal cell carcinoma, including systemic therapy in the adjuvant or neoadjuvant setting, immunotherapy, investigational therapy, surgical metastaticity, or radiation therapy.
- b. Patients must not be planning to receive other anti-cancer agents including investigational agents while on protocol treatment.
- c. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- d. Patients must not have received immunization with an attenuated live vaccine within seven days prior to registration nor have plans to receive such vaccination while on protocol treatment.



- e. Patients must not be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors, (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, fluvoxamine, nefazodone, nelfinavir, ritonavir) and/or strong CYP3A4 inducers (e.g. phenytoin, rifampin, rifabutin) within 14 days prior to randomization. (Moderate inhibitors or inducers of isoenzyme CYP3A4 should be avoided, but if necessary can be used with caution. See [Section 7.1c.](#))

### 5.3 Clinical/Laboratory Criteria

- a. Patients must have a complete physical examination and medical history within 28 days prior to registration.
- b. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia. See [Appendix 18.1.](#)
- c. Patients must not have any known uncontrolled underlying pulmonary disease (e.g. FEV1 or DLCO 50% or less of predicted **OR** O2 saturation 88% or less at rest on room air).
- d. Patients must not have any known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients.
- e. Patients must have absolute neutrophil count (ANC)  $\geq 1,500/\text{mcl}$ , platelet count  $\geq 100,000/\text{mcl}$  and hemoglobin  $\geq 9.0 \text{ g/dl}$  obtained within 28 days prior to registration.
- f. Patients must have serum creatinine  $\leq 2.0 \times$  upper limit of normal (ULN) or calculated creatinine clearance (CrCl)  $\geq 30\text{mL}/\text{min}$  obtained within 28 days prior to registration.

$$\text{Calculated creatinine clearance} = \frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$$

- g. Patients must have bilirubin  $\leq 1.5 \times$  ULN, and SGOT and SGPT  $\leq 2.5 \times$  ULN obtained within 28 days prior to registration.
- h. Patients must NOT have liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh Class C). NOTE: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV and HCV testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection. (See [Section 9.0](#) for testing information and [Section 8.6](#) for management of patients with positive testing.)
- i. Patients must not have a known history of HIV seropositivity.
- j. Patients must not have uncontrolled hyperlipidemia (fasting serum cholesterol  $>300 \text{ mg/dL}$  AND fasting triglycerides  $> 2.5 \times$  ULN) obtained within 28 days prior to registration. Optimal lipid control must be achieved before registration and monitored during protocol treatment (see [Section 8.4b.](#))
- k. Patients must not have uncontrolled diabetes mellitus (defined by fasting serum glucose  $> 1.5 \times$  ULN) obtained within 28 days prior to registration. Optimal



glucose control must be achieved before registration and monitored during protocol treatment (see [Section 8.4b](#)).

- l. Patients must be able to take oral medications. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
- m. Patients must have a Zubrod Performance Status of 0 or 1 (see [Section 10.3](#)).
- n. All patients must be 18 years of age or older.
- o. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- p. Patients must not be pregnant or nursing due to animal studies that have shown reproductive toxicity effects. Women/men of reproductive potential must have agreed to use an effective contraceptive method during protocol treatment and up to 8 weeks after ending protocol treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

#### 5.4 Translational Medicine Criteria

- a. Patients must be offered the opportunity to participate in specimen banking for future use to include the translational medicine studies outlined in [Section 15.0](#).

#### 5.5 Regulatory Criteria

- a. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- b. As part of the OPEN registration process (see [Section 13.4](#) for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

## 6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm (45) with stratification based on:

- a. Risk group based on pathologic stage (intermediate high-risk vs very high risk) (see [Section 4.0](#)),
- b. Histology (clear cell vs non-clear cell); (NOTE: The tumor will be classified as clear cell if **any** component of clear cell histology is identified in the specimen.)
- c. Performance status (0 vs 1).

## 7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Christopher Ryan at 503/494-8487 or Dr. Elisabeth Heath at 313/576-8715. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

### 7.1 Good Medical Practice

The following tests (and/or assessments) are recommended within 28 days prior to registration in accordance with Good Medical Practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests/assessments that could impact on patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Chair prior to registering.

- a. Patients should not have an uncontrolled intercurrent illness including, but not limited to active bleeding diathesis, uncontrolled infection/disorders, nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy, or psychiatric illness/social situations that would limit compliance with study requirements.
- b. Testing for hepatitis B viral load and serologic markers: HBV-DNA, HBsAg, HBs Ab, and HBc Ab should be performed at screening for all patients with the following risk factors (see [Section 7.3](#) and [8.6](#)):
  - Patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, and Greece.
  - known or suspected past hepatitis B infection,
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - current or prior high-risk sexual activity,
  - body piercing (other than ear piercing) or tattoos,
  - mother known to have hepatitis B
  - history suggestive of hepatitis B infection, e.g., dark urine, jaundice, right upper quadrant pain.
  - Additional patients at the discretion of the investigator
  - household contact with hepatitis B infected patient(s),

Testing for hepatitis C should be performed using quantitative RNA-PCR at screening for patients with the following risk factors (see [Section 8.6](#)):





- known or suspected past hepatitis C infection (including patients with past interferon 'curative' treatment),
  - blood transfusions prior to 1990,
  - current or prior IV drug users,
  - current or prior dialysis,
  - household contact of hepatitis C infected patient(s),
  - current or prior high-risk sexual activity,
  - body piercing other than ear piercing or tattoos,
  - Additional patients at the discretion of the investigators
- c. Coadministration of moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and inducers (such as bamazepine, phenobarbital) should be avoided if possible, or used subject to caution. Coadministration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided if possible, or used subject to caution. See [Appendix 18.3](#). Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should be avoided.
- d. Alkaline phosphatase obtained.

## 7.2 Treatment Schedule

All patients will be randomized to receive either everolimus or placebo daily for nine, six week cycles.

AGENT	DOSE	ROUTE	DAYS	DURATION
Everolimus or Matched Placebo	10 mg (two 5 mg Tablets)	Oral	Every Day	378 days (54 weeks)

\* Everolimus (or matched placebo) tablets are supplied as 5 mg tablets.

Everolimus must be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets must be swallowed whole with a glass of water. The tablets must not be chewed or crushed, and grapefruit or citrus juices should be avoided.

A cycle of treatment is six weeks. Assessment for the primary endpoint (recurrence) must occur after every three cycles (18 weeks) for 54 weeks, then every six months for two years, and then annually thereafter until recurrence, death, or 10 years after registration, whichever comes first (regardless whether patient is still on active protocol treatment). Recurrence assessments consist of physical exams and CT scans.

Radiographic assessment for pneumonitis must be undertaken as per [Section 8.4c](#).

## 7.3 Concomitant Therapy

All medications taken other than study drugs and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy must be documented in the "comments" section of the **S0931** Treatment Form.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics ± steroids), with the following exceptions:





- No other investigational therapy must be given to patients.
- No chronic treatment with systemic steroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- No anticancer agents other than the study medications administered as part of this study protocol must be given to patients. If such agents are required for a patient then the patient must be withdrawn from protocol treatment.
- Growth factors (e.g. G-CSF, G-GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.
- Live vaccines must not be administered to patient due to immunosuppressant potential of everolimus.
- Drugs known to be strong inhibitors or inducers of the isoenzyme CYP3A4 must not be administered as systemic therapy (see [Section 5.2e](#)). Drugs or substances known to be moderate inhibitors or inducers of CYP3A (see [Appendix 18.3](#)) should be avoided if possible or used subject to caution as these can alter everolimus metabolism. Co-administration with strong or moderate inhibitors of P-glycoprotein (PgP) (see [Appendix 18.3](#)) should be avoided if possible, or used subject to caution. Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.
- It is highly recommended that patients positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug (see [Section 8.5](#)).
- The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug.
- Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule (See [Section 8.6](#) and [9.0](#)).

#### 7.4 Intake Calendar

Everolimus drug compliance will be recorded on a treatment Intake Calendar (see [Appendix 18.4](#)). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Sites utilizing the CIRB must use the Intake Calendar provided. Sites not utilizing the CIRB may use institutional pill diaries or other source documentation in place of Intake Calendar at the discretion of the treating physician.

#### 7.5 Unblinding Procedures

The procedures for emergency unblinding are outlined in [Appendix 18.2](#). Patients who have recurrence of disease as defined in [Section 10.1](#) have the option to be unblinded in planned fashion, as described in this section. Emergency unblinding will be done for anything other than recurrence as defined in [Section 10.1](#). Patients who undergo optional treatment unblinding and are found to have been randomized to “placebo” will not receive investigational-supplied everolimus. Novartis Pharmaceutical Corporation will NOT provide investigational supplies of everolimus once a patient has been unblinded.

##### a. Criteria for Planned Unblinding:

The planned unblinding procedure applies to patients who experience recurrence as defined in [Section 10.1](#). It is vital to properly apply the protocol specified definition of recurrence. If any questions arise with regard to recurrence for a patient, please contact the GU Data Coordinator in Seattle by e-mail at [guquestion@crab.org](mailto:guquestion@crab.org) or by telephone at 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

Prior to requesting a planned unblinding, the following forms must be submitted and processed by the SWOG Data Operations Office:



Off Treatment Notice

**S0931** Recurrence Assessment Form

Radiology report(s) supporting recurrence (see [Section 10.1](#))

Pathology report(s) supporting recurrence (see [Section 10.1](#))

Please submit all required forms to the SWOG Data Operations Center ([guquestion@crab.org](mailto:guquestion@crab.org)) with the subject line "**S0931** Patient #XXXXXX, Requesting Planned Unblinding". Please allow a minimum of 2 working days for review of forms.

Dr. Ryan (or Heath) will provide a written confirmation to the site that the patient has an adequately documented recurrence. This documentation should be placed in the patient's chart.

b. Planned Unblinding Procedures

You may unblind patients at time of disease recurrence from Member, Affiliate, and CCOP institutions to a Therapeutics study using the SWOG planned unblinding program. To access the planned unblinding program go to the SWOG Web site (<http://swog.org>) and click on the *Logon* link to go to the SWOG Members Area logon page (<https://swog.org/members/logon.asp>). This Web program is available at any time except for periods listed under *Down Times*. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at <https://swog.org/members/logonhelp.asp>. After you have logged on, click on the *Workbenches* link, then the *CRA Workbench* link, and then the *Planned Unblinding* link. Go to the Entry Page for the Planned Unblinding program. The CRA must have the SWOG ID number, initials, and investigator number available for the unblinding.

To unblind a patient at disease recurrence, you must meet the following criteria (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number.
2. You are associated as an investigator or CRA/RN to the institution where a planned unblinding is occurring.
3. You are granted permission to use the Planned Unblinding program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users.

Non-SWOG sites may unblind patients at time of disease recurrence using the following url: <https://crawb.crab.org/TXWB/ctsulogon.aspx>.

If the Web Planned Unblinding program is not used, the planned unblinding must be done by phone.

Member, Affiliate and CCOP Institutions

Planned unblinding by phone of patients from Member, Affiliate and CCOP institutions must be done through the SWOG Data Operations Center in Seattle by telephoning



206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

NOTE: When unblinding **S0931** patients in the SWOG Planned Unblinding Program leave "Bottle ID" field blank.

#### 7.6 Criteria for Removal from Protocol Treatment

- a. Recurrence of disease or symptomatic deterioration (as defined in [Section 10.0](#)). If the patient has documented recurrence as defined in [Section 10.1](#), unblinding of study treatment as outlined in [Section 7.5](#) may be requested.
- b. Unacceptable toxicity defined as any toxicity requiring discontinuation of study drug per [Section 8.0](#). If a patient is removed from protocol treatment due to toxicity, he/she must continue to be followed for recurrence according to the same schedule as detailed in [Sections 7.2](#) and [9.0](#) (every 4 months [18 weeks] during Year 1 (regardless whether patient is still on active protocol treatment), then every six months for Years 2 and 3, and then annually thereafter until recurrence, death, or 10 years after registration, whichever comes first. Recurrence assessments consist of physical exams and CT scans)
- c. Delay in protocol treatment > 21 days due to pneumonitis or > 28 days due to any other reason. If a patient is removed from protocol treatment due to toxicity, the must continue to be followed for recurrence according to the same schedule as detailed in [Sections 7.2](#) and [9.0](#) (every 4 months [18 weeks] during Year 1 (regardless whether patient is still on active protocol treatment), then every six months for two years, and then annually thereafter until recurrence, death, or 10 years after registration, whichever comes first. Recurrence assessments consist of physical exams and CT scans)
- d. Completion of nine cycles of protocol treatment.
- e. The patient may withdraw from the study at any time for any reason.

#### 7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

#### 7.8 Follow-Up Period

All patients will be followed for a maximum of 10 years after registration or until death (whichever occurs first) for recurrence and survival.

## 8.0 DOSE MODIFICATIONS

### 8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

### 8.2 General Dose Modification Considerations

- a. Missed doses are to be omitted rather than made up.
- b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.



- c. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.
- d. Once dose is reduced, patients will continue at new dose. No dose re-escalations are allowed.
- e. If protocol treatment is held > 21 days for pneumonitis or > 28 days due to any other reason, patient should be removed from protocol treatment.

8.3 Everolimus Dose Levels

Dose Levels	Dose
Full	10 mg daily (two 5 mg tablets)
-1 Level	5 mg daily
-2 Level	5 mg every other day
-3 Level	Discontinue study drug

8.4 Everolimus Dose Modifications

**NOTE: NO DOSE ESCALATION OR RE-ESCALATION IS ALLOWED.**

Toxicity	Actions
<b>Non-hematological toxicity</b>	
Grade 2 (except pneumonitis – see <a href="#">8.4.c</a> ) (except hyperlipidemia – see <a href="#">8.4.b</a> )*	If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at same dose. If event returns to Grade 2, then interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one lower dose level.
Grade 3 (except pneumonitis – see <a href="#">8.4.c</a> ) (except hyperlipidemia – see <a href="#">8.4.b</a> )*	Interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue everolimus.
<b>Hematological toxicity</b>	
Grade 2 Thrombocytopenia (platelets < 75, ≥ 50x10 <sup>9</sup> /L)	Interrupt everolimus until recovery to Grade ≤1 (≥ 75 x10 <sup>9</sup> /L). Then reintroduce everolimus at same dose. If thrombocytopenia again returns to Grade 2, interrupt everolimus until recovery to Grade ≤1. Then reintroduce everolimus at one lower dose level.
Grade 3 Thrombocytopenia (platelets < 50, ≥ 25x10 <sup>9</sup> /L)	Interrupt everolimus until recovery to Grade ≤ 1 (platelets ≥ 75 x10 <sup>9</sup> /L). Then resume everolimus at one lower dose level. If Grade 3 thrombocytopenia recurs, discontinue everolimus.
Grade 4 Thrombocytopenia (platelets < 25 x10 <sup>9</sup> /L)	Discontinue everolimus.

Toxicity	Actions
<b>Non-hematological toxicity</b>	
Grade 3 Neutropenia (neutrophils < 1, $\geq 0.5 \times 10^9/L$ )	Interrupt everolimus until recovery to Grade $\leq 1$ (neutrophils $\geq 1.5 \times 10^9/L$ ). Then resume everolimus at the same dose. If ANC again returns to Grade 3, hold everolimus until the ANC $\geq 1.5 \times 10^9/L$ . Then resume everolimus at one lower dose level. Discontinue patient from study therapy for a third episode of Grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < $0.5 \times 10^9/L$ )	Interrupt everolimus until recovery to Grade $\leq 1$ (neutrophils $\geq 1.5 \times 10^9/L$ ). Then resume everolimus at one lower dose level. If Grade 3 or Grade 4 neutropenia occurs despite this dose reduction, discontinue everolimus.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt everolimus until resolution of fever and neutropenia to Grade $\leq 1$ . Hold further everolimus until the ANC $\geq 1,500/mm^3$ and fever has resolved. Then resume everolimus at one lower dose level. If febrile neutropenia recurs, discontinue everolimus.
Grade 4 febrile neutropenia (life-threatening)	Discontinue everolimus.

\* Grade 2-3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see [Section 8.4b](#)).

If a patient requires a dose delay of > 21 days for pneumonitis or > 28 days for any other reason from the intended day of the next scheduled dose, then the patient must be removed from the protocol treatment.

a. Hematological Toxicity

No dose adjustments are recommended for anemia. The treating physician may hold everolimus for anemia if it is felt to be in the best interest of the patient. Aranesp (darbepoetin alfa) and Procrit (epoetin alfa) are not indicated for anemia. If patient does not recover after 28 days of holding drug then the patient must be removed from treatment.

Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelet growth factors, etc.) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.

b. Hyperlipidemia and Hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or greater hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 or greater hypertriglyceridemia (> 300 mg/dL - 500 mg/dL; >3.42 mmol/L- 5.7 mmol/L) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk



versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy. The fasting state of patients should be verified when interpreting results. It is suggested that optimal glucose control should be achieved before starting a patient on everolimus and should be monitored during everolimus therapy.

c. Pneumonitis

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic.

Both asymptomatic and symptomatic non-infectious pneumonitis have been noted in patients receiving everolimus. 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 medical causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

In order to monitor for asymptomatic non-infectious pneumonitis, the regularly scheduled chest CTs for disease surveillance should be assessed for evidence of pneumonitis during protocol treatment. Additional chest CT scans may be performed, when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered.

Management of Non-Infectious Pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1	CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required	Administer same dose of everolimus.
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce everolimus one dose level until recovery to ≤ Grade 1. Everolimus may also be interrupted if symptoms are troublesome.



Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
	*		Patients will be removed from protocol treatment if they fail to recover to $\leq$ Grade 1 within 21 days.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to $\leq$ Grade 1. May restart protocol at one lower dose level. Patients will be removed from protocol treatment if they fail to recover to $\leq$ Grade 1 within 21 days.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O <sub>2</sub> saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

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\*A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

d. Oral Mucositis

In addition to the dose modifications for non-hematological toxicity outlined in [Section 8.4](#), oral mucositis due to everolimus should be treated using local supportive care. Follow the paradigm below for treatment of oral mucositis:

1. For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).



3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, thereby leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

e. Nausea

Routine premedication for nausea is not necessary, but symptomatic patients should be treated with standard anti-nausea/antiemetic therapy as necessary.

If the patient vomits after taking the tablets, the dose is replaced only if the tablets can actually be seen and counted.

f. Diarrhea

Diarrhea has been seen with everolimus. In general, diarrhea has been transient, usually not of sufficient severity to hinder administration of everolimus and responsive to loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg PO q 2-4 hours until diarrhea free for 12 hours.

8.5 Infection Precaution

Everolimus has immunosuppressive properties and may predispose patients to infections, especially those with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jirovecii pneumonia (PJP) 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, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly.

8.6 Management of Hepatitis Reactivation

In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anticancer therapy has been shown to reduce the risk of hepatitis B virus (HBV) reactivation and associated HBV morbidity and mortality. (*Lomba et al. 2008*)

**Monitoring and prophylactic treatment for hepatitis B reactivation**

[Table 1](#) provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

**Table 1 Action to be taken for positive baseline hepatitis B results**

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBs Ab	+ or -	+ or -	+	+ or -	- or + with prior HBV
			and no prior HBV		





Test	Result	Result	Result	Result	Result
			vaccination		vaccination
HBc Ab	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of study drug  Monitor HBV-DNA approximately every 4-6 weeks		No prophylaxis  Monitor HBV-DNA approximately every 4-6 weeks		No specific action

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of study drug.

For hepatitis B reactivation, definition and management guidelines, see [Table 2](#) Guidelines for management of hepatitis B.

**Table 2 Guidelines for management of hepatitis B**

HBV reactivation (with or without clinical signs and symptoms)*	
<p>For patients with baseline results: Positive HBV-DNA OR positive HBsAg ----- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA] AND ALT elevation x 5 ULN</p>	<p>Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ Grade 1 ALT (or baseline ALT, if &gt; Grade 1) and ≤ baseline HBV-DNA levels  If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug.  If resolution occurs &gt; 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.</p>
<p>For patients with baseline results: Negative HBV-DNA and HBsAg AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab] -----</p>	<p>Treat: Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels  If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of study drug 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 study drug.</p>

HBV reactivation (with or without clinical signs and symptoms)*	
reactivation is defined as: New appearance of measurable HBV-DNA	If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

\* All reactivations of hepatitis B are to be recorded as Grade 3 (CTCAE v 4.0 Infections and Infestations: Hepatitis Viral), unless considered life threatening by the investigator; in which case they should be recorded as Grade 4 (CTCAE 4.0 Infections and Infestations: Hepatitis Viral). Date of viral reactivation is the date on which **both** DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached  $\geq 5 \times$  ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

### Monitoring for Hepatitis C

The following two categories of patients should be monitored every 4-6 weeks for HCV reactivation:

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

For definition of hepatitis C reactivation and the management guidelines, see [Table 3](#) Guidelines for management of hepatitis C.

**Table 3 Guidelines for management of hepatitis C**

HCV reactivation*	
For patients with baseline results: Detectable HCV-RNA,  reactivation is defined as: ALT elevation x 5 ULN	Discontinue study drug
For patients with baseline results: Knowledge of past hepatitis C infection with no detectable HCV- RNA,  reactivation is defined as: New appearance of detectable HCV- RNA	Discontinue study drug

\* All reactivations of hepatitis C are to be recorded as Grade 3 (CTCAE 4.0 Infections and Infestations: Hepatitis Viral), unless considered life threatening by the investigator; in which case they should be recorded as Grade 4 (CTCAE 4.0 Infections and Infestations: Hepatitis Viral).

#### 8.7 Emergency Unblinding

For emergency unblinding guidelines see [Section 18.2](#).

#### 8.8 Dose Modification Contacts

For treatment or dose modification related questions, please contact Dr. Christopher Ryan at 503/494-8487 or Dr. Elisabeth Heath at 313/576-8715.

#### 8.9 Adverse Event Reporting



Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in [Section 16.0](#) of the protocol must be reported to the Operations Office, Study Chair, the NCI via CTEP-AERS, and to the IRB per local IRB requirements.



9.0 STUDY CALENDAR

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REQUIRED STUDIES	PRE STUDY	Cycle 1						Cycle 2		Cycle 3 §		Off Treat F/U Prior to Recurrence	Recurrence	Off Treat F/U After Recurrence
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7 ----->12	WK	WK 13 ----->18	WK			
<b>PHYSICAL</b>														
History and Physical Exam	X*	XЯ			X			X		X		X	X	X
Hepatitis B/C Screening †	X													
Weight and Performance Status	X	XЯ						X		X				
Recurrence Assessment ¶ Ж											X	X¶	X	
Toxicity Notation Ω		X	X	X	X	X	X	X		X				
Review Intake Calendar								X		X				
<b>LABORATORY</b>														
WBC/Differential /Platelets	X							X		X				
Hemoglobin	X							X		X				
Bilirubin	X							X		X				
SGOT and SGPT	X							X		X				
Serum Creatinine or Calculated Creatinine Clearance	X							X		X				
Alkaline Phosphatase	X							X		X				
Fasting Glucose, Cholesterol and Triglycerides	X							X		X				
HBV DNA or HCV RNA-PCR Δ								X		X				

Study Calendar continued on next page. Click here for [footnotes](#).



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REQUIRED STUDIES	PRE STUDY	Cycle 1						Cycle 2		Cycle 3 §		Off Treat F/U Prior to Recurrence	Recurrence	Off Treat F/U After Recurrence
		WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7 ----->12	WK 13 ----->18	WK	WK			
<b>SPECIMEN SUBMISSION ¶</b>														
Archived Tumor Specimen	X													
Buffy Coat and Plasma Specimens	X							X		X		X	X	
Whole Blood for Trough Levels	X							X		X		X		
<b>X-RAYS AND SCANS</b>														
CT Scan of Chest/Abdomen/Pelvis £ ¶	X										X £ ¶	X	X	
Bone Scan ¶	X¶											X¶		
<b>TREATMENT</b> (see Section 7.0 for details)														
Everolimus/Placebo		X ----->X												

Click here for [footnotes](#).



FOOTNOTES:

**NOTE: Forms are found in [Section 18.0](#). Forms submission guidelines may be found in [Section 14.0](#).**

- \* Physical exam and medical history must be completed within 28 day prior to registration (see [Section 5.3a](#)).
- Δ Only for patients with positive HBV or HCV studies at baseline (see [Section 8.6](#)).
- † An assessment of Hepatitis B/C medical history and risk factors must be done at screening (see [Section 5.3h](#)). Patients with risk factors for Hepatitis B should undergo HBV DNA, HBsAg, HBsAb, and HBcAb testing (see [Sections 7.1, 7.3](#) and [8.6](#)). Patients with risk factors for Hepatitis C infection should undergo HCV RNA-PCR testing (see [Sections 7.1](#) and [8.6](#)).
- § Protocol treatment will continue at the same intervals indicated for Cycle 3 for a maximum of 9 cycles (54 weeks) or until the patient has met any of the criteria listed in [Section 7.6](#).
- √ After recurrence, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for the first two years and then yearly thereafter until 10 years after registration.
- £ CT scans of the chest must also be assessed for radiographic evidence of pneumonitis (see [Section 8.4c](#)).
- Ж Scan (CT scan of the chest, abdomen and pelvis with IV and oral contrast; CT scan of chest without contrast and MRI of abd/pelvis with gadolinium) and recurrence assessment must be performed every 4 months (18 weeks) during Year 1 (regardless of early protocol treatment discontinuation), every 6 months for Years 2 and 3, and yearly thereafter until recurrence, death, or 10 years after registration whichever comes first.  
The surveillance imaging therapy intervals prescribed here are considered standard of care by expert consensus (SWOG Genitourinary Committee) based on the high risk of cancer recurrence in the patients enrolled in this study. Non-contrast CT of the chest/abdomen/pelvis should only be used for surveillance imaging if, in the opinion of the investigator, it is in the best medical interest of the patient to not receive IV contrast of any form.  
NOTE: PET/CT is not an acceptable imaging alternative.
- ¥ See [Section 15.0](#). If patient has consented to banking for the translational medicine component, it is very important to obtain whole blood for trough levels and buffy coat and plasma specimens from any patient that is being removed from protocol treatment, regardless of the time point. DO NOT COLLECT SPECIMENS AT EACH VISIT DURING FOLLOW-UP. Additionally, specimens for buffy coat and plasma specimens should be collected at disease recurrence. **Specimens must be drawn prior to daily dose of study drug.**
- Ω Once everolimus treatment has been initiated, weekly toxicity assessments are required during the first cycle. Toxicity assessments during the first cycle may be performed via a phone call during weeks when a physical exam is not required.
- Н Bone scan recommended if patient has rising alkaline phosphatase or bone pain.
- Я If prestudy history and physical exam, weight and performance status are obtained within 28 days prior to registration, they do not need to be repeated for Cycle 1, Day 1.
- ¶ If patient is taken off protocol treatment due to toxicity or other reason besides recurrence, they must continue to be followed for recurrence with physical exams and scans every 4 months (18 weeks) during Year 1 (regardless of early protocol treatment discontinuation), every 6 months for Years 2 and 3, and yearly thereafter until recurrence, death, or 10 years after registration whichever comes first.



## 10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

### 10.1 Recurrence

See [Section 9.0](#) for recurrence assessment schedule.

The following are the only acceptable criteria for renal cell cancer recurrence. Anything not listed as acceptable should not be an indication to alter protocol therapy. Any recurrence of malignant disease should be proven by tissue biopsy whenever possible. Supporting documentation must be submitted following diagnosis of renal cell carcinoma recurrence.

The following criteria of treatment failure constitute the only acceptable evidence of disease recurrence. Supporting documentation includes a copy of radiology and pathology reports.

Lung: (i) positive cytology or biopsy in the presence of a solitary lesion, (ii) radiologic evidence of multiple lesions felt to be consistent with metastases. (iii) neoplastic pleural effusion should be established by cytology or pleural biopsy.

Liver: (i) positive cytology or biopsy (ii) multiple new focal defects on MRI scan, CT or ultrasound that are enlarging in size as documented by repeat scans. (iii) proof of neoplastic abdominal ascites should be established by cytology or pleural biopsy.

Central Nervous System: positive brain CT scan or MRI scan or cerebral spinal fluid cytology.

Subcutaneous and Lymph Node Recurrence: (i) positive biopsy (ii) progressively enlarging solid mass or node(s) as evidenced by repeat CT or MRI scans (iii) ureteral obstruction in the presence of a mass as documented on CT or MRI scan.

Other Organs: (i) positive radiographic study and biopsy/aspiration cytology (ii) progressively enlarging solid mass or node(s) as evidenced by repeat CT or MRI scans.

Renal Bed: (i) positive radiographic study and biopsy/aspiration cytology (ii) progressively enlarging solid mass or node(s) as evidenced by two CT or MRI scans separated by at least a 4 week interval.

Skeletal: (i) positive radiographic study such as bone scan, (ii) for a solitary lesion or equivocal finding on scan, a biopsy is required to demonstrate recurrence, (iii) MRI or CT of solitary or equivocal lesion seen on bone scan that confirms metastasis is also acceptable.

### 10.2 Symptomatic deterioration

Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.



### 10.3 Performance Status

Patients will be graded according to the Zubrod performance status scale.

<u>POINT</u>	<u>DESCRIPTION</u>
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

### 10.4 Recurrence-Free Survival

From date of registration to date of first documentation of recurrence outlined in [Section 10.1](#) or death due to any cause. Patients last known to be alive and recurrence-free are censored at date of last contact.

### 10.5 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

## 11.0 STATISTICAL CONSIDERATIONS

### 11.1 Accrual Goal

ECOG's ASSURE trial randomized on average, 480 patients per year (40 per month). To be slightly more conservative, we anticipate that 28 patients per month (336 per year) will be randomized to this study. Based on the distribution of risk groups observed on **E2805** including half of the patients falling into the very-high risk group, it will be assumed that the placebo arm will produce a median recurrence-free survival of 4.9 years. **E2805** has also experienced a significant proportion of patients who have not completed the one year of protocol-specified treatment. Based on data from a recent amendment to **E2805**, twenty-five percent of patients have withdrawn from treatment on this study within the first three months. Although we expect everolimus to be better tolerated than sorafenib or sunitinib, we would estimate that about 15% of patients will stop protocol treatment within the first three months. Using a weighted average of the log hazard rates to obtain the effective hazard rate for the treatment arm under the alternative hypothesis, the ideal hazard ratio (HR) of 0.75 becomes an effective hazard ratio of 0.78 when lack of compliance is considered. Assuming exponential survival, 3.5 years of patient accrual, four additional years of follow-up and a sample size of 1170 patients (585 experimental, 585 placebo), the study has 85% power to detect a 22% reduction in the hazard rate of recurrence-free survival with everolimus compared to placebo (hazard ratio 0.78). This corresponds to an improvement in the median RFS from 4.9 to 6.3 years if the RFS





distributions are exponential. We will use a one sided stratified log rank test with  $\alpha = 0.025$ .

July 2015 Revision: As we now have a large amount of data to evaluate the rate of compliance to everolimus, we see that our original assumption of a 15% non-compliance rate was an underestimate. We propose to adjust the study design based on the observed compliance data from this trial in consultation with the study Data and Safety Monitoring Committee, and based on the following assumptions: those who receive less than 3 months of study drug have the same risk of recurrence as the placebo group, and those who receive 3-6 months of study drug have half the treatment benefit as those who receive more than six months.

We still assume an ideal HR=0.75, but we increase the accrual duration by one year to 4.5 years, and keep 4 years of follow-up. We are also reducing the statistical power from 85% to 80% in order to achieve a sample size that seems achievable within a reasonable amount of time. By making the prior assumptions about treatment efficacy, we will have an effective HR of 0.82 based on the proportion of dropouts and when they became noncompliant.

Assuming exponential recurrence-free survival, 4.5 years of patient accrual, four additional years of follow-up and an updated sample size of 1464 eligible patients (732 per arm), the study has 80% power to detect a 18% reduction in the hazard rate of recurrence free survival with everolimus compared to placebo (HR=0.82). This corresponds to an improvement in the median RFS from 4.9 to 6.0 years if the RFS distributions are exponential. We will use a one sided stratified log rank test with  $\alpha=0.025$ .

## 11.2 Analysis of Primary Endpoint

This study's design is based on assumptions about the accrual rate, the distribution of intermediate-high and very-high risk patients that have been randomized on ASSURE and histology. The total projected accrual adjusted for a 5% ineligibility rate is 1,537 patients (previously 1,218). If accrual to the intermediate-high risk strata reaches 50% of the total projected accrual then the stratum will be closed to further accrual. If accrual to the clear cell histology stratum reaches 85% of the total projected accrual then the stratum will be closed to further accrual. This will ensure accrual patterns in the strata with high event rates are comparable to those assumed in the study design. If the event rate information becomes available from ASSURE, the study team may consider recommending that the sample size be reevaluated. The sample size adjustment would be based on baseline characteristics. Only the number of patients accrued would possibly change, but the number of events and formal analysis timepoints, which are based on number of events, would not change.

The first interim analysis will be conducted after approximately 1,000 patients have been entered ( $n=500$  per arm), approximately 4 years after the study opens and when 30% of the expected number of recurrences have occurred on the placebo arm. A second interim analysis will be conducted approximately 5 years after the study opens and when 50% of the expected events on the placebo arm have been observed. The third interim analysis will be conducted when 70% of the expected events on the placebo arm have been observed. The fourth interim analysis will occur approximately 7.5 years after study activation when 90% of the expected events on the placebo arm have been observed. For each interim analysis, timing of analysis will be based on percent of expected information and not on calendar time. Evidence suggesting early termination of the trial and a conclusion that everolimus is not better than placebo would be if the alternative hypothesis of a 22% improvement in recurrence-free survival with the experimental arm is rejected at the 0.002 level. In addition, the null hypothesis of no difference in recurrence-free survival will be tested at the one-sided level of 0.001. If the decision is to continue the study to completion, the final analysis will be done after complete accrual



and approximately four years of follow-up at complete information when 804 total events have occurred across both arms. A stratified, one-sided log-rank test will be used for testing the primary hypothesis at the 0.022 level to account for interim testing.

December 2020 Update:

The expected endpoint rate in the placebo arm is lower than anticipated. Although three interim analyses have been conducted to date, the number of events is slowing making it difficult to reach the targeted number of events. Therefore, we consider some modification to the statistical analysis plan. This plan was developed by two independent biostatisticians who had not seen and had no access to endpoint data for this trial, with medical input from the primary study chair. The SWOG Data and Safety Monitoring Committee reviewed and approved this revision

The median recurrence-free survival of ASSURE (6.6 years) was longer than the six years assumed for this trial so the actual number of events in the placebo arm may be less than originally projected.

To keep power at 80% under current trial conditions, we continue to use the 4.5 years of accrual but allow 6 additional years of follow-up after the last accrual for a total of 10.5 years. Assuming a more conservative control arm hazard rate of 0.1027 (median RFS=6.75 years), the expected date of data maturity (804 total events) under the alternative hypothesis is September 2021. However, the necessary 804 events may never be attained because of drop out or failure of the underlying exponential distribution assumption and so the final analysis is expected in March 2022 even if 804 events have not been observed. In addition, the 4<sup>th</sup> and final interim analysis should be conducted one year prior in March 2021 regardless of the percent of expected information. The futility analysis is being changed from a one-sided 0.001 to a 1-sided value of 0.025 in the last interim analysis. This will have minimal effect on power if the true hazard ratio is 0.82 but would lead to earlier reporting if the observed hazard ratio is close to 1.0.

Updated Timing of Scheduled Analyses on **S0931, December 2020 Update**

Analysis	Estimated Study Time	# of Events on Placebo Arm* (% of total expected)	# of Events on Everolimus Arm (assuming Ha)	Testing Ho, Level of significance	Testing Ha, Level of significance
1 <sup>st</sup> interim analysis	4 years after activation	119 (30%)	104	.002	.001
2 <sup>nd</sup> interim	5 years after activation	208 (50%)	183	.002	.001
3 <sup>rd</sup> interim	6 years after activation	297 (70%)	264	.002	.001
4 <sup>th</sup> interim		March 2021		.002	.025
Final analysis		422 (100%)#	382#	0.022	N/A

\* timing of all planned analyses is based on the number of events in this column

# timing of final analysis at 804 total events or a maximum time of March 2022

11.3 Analysis of Secondary Endpoints

Secondary analyses will be performed for comparison between the two arms regarding survival and adverse events. With 732 patients on each arm, toxicity rates can be estimated to within at worst  $\pm 3.7\%$  (95% confidence interval). Additional exploratory analyses will include assessing the treatment effect within subgroups defined by the stratification factors as well as the interaction of everolimus with each of the stratification



factors, and whether the surgery was partial or a radical nephrectomy. With at least 15% of the patients having non-clear cell histology, for this subgroup the difference in the survival rates between the treatment arms can be estimated to within at worst  $\pm 5\%$  (95% confidence interval).

#### 11.4 Analysis of Translational Medicine Endpoints

(A) Prognostic significance: Proportional hazards regression will be used to evaluate the association between genes and pathways and recurrence-free survival and overall survival. Additional exploratory methodology may include classification and regression trees or logic regression to identify combinations of markers that may be associated with the endpoints of interest. The following table shows the minimally detectable RFS hazard ratio for various prevalence of markers and rates of sample submission with 80% statistical power and a two-sided  $\alpha=0.05$ . This table assumes no treatment by marker interaction, and a median RFS of 4.9 years in those with the biomarker of interest.

Minimally Detectable Hazard Ratios for Recurrence-Free Survival

	sample submission (n=1170)	sample submission (n=936)	sample submission (n=702)
10% prev of a SNP	1.46	1.52	1.63
20% prev. of a SNP	1.33	1.38	1.45
30% prev. of a SNP	1.28	1.32	1.38

(B) Predictive significance: In order to evaluate whether molecular biomarkers in the AKT/mTOR pathway are predictive factors for everolimus, we will assess the interaction of the biomarker with treatment in a proportional hazards regression model assessing RFS. The entry in the following table is the minimally detectable ratio of the HR's of placebo/everolimus for those without the pathway activation relative to those that do have the activation. For simplicity of calculations, we assume that there is no prognostic association of biomarker activation and RFS in the placebo group, and the treatment effect for those without activation is null. That is, everolimus only has an impact on RFS among those with marker activation.

Minimally Detectable Interaction for Recurrence-Free Survival

Table entry is the hazard ratio of (Everolimus/Placebo) for those without marker activation relative to the HR of (Ever/PI) for those with marker activation, assuming 80% statistical power and a two-sided $\alpha=0.05$			
	100% sample submission	80% sample submission	60% sample submission
10% prev. of a marker	2.40	2.75	3.49
20% prev. of a marker	1.85	2.00	2.28
30% prev. of a marker	1.68	1.80	1.99

If 936 of patients randomized to this trial provide a usable tissue sample for these translational objectives, and the prevalence of the biomarker of interest is 20%, then we will have reasonable power (80%) to detect a hazard ratio of approximately 0.50 for those with a marker compared to a HR of 1.0 for those without the marker ( $1.0/0.50 = 2.00$ ). Frequency and severity of adverse events and proximity to sample collection will be correlated with steady-state  $C_{min}$ . Assuming 90% of those randomized to everolimus will submit one or more serum samples, we will have approximately 526 subjects to analyze.



Initially, correlations of adverse events and the  $C_{min}$  in closest proximity to the adverse event will be explored in a manner analogous to multiple t-tests. Logistic regression modeling will be used to assess whether  $C_{min}$  is a predictor for the presence of the adverse events after adjusting for other patient and disease covariates. Proportional odds (PO) models may be used to model severity of an adverse event in ordinal categories, if the PO modeling assumption is supported by the data.

#### 11.5 Pharmacokinetic Analysis of Blood Samples

For the pharmacokinetic analysis of blood samples, we will use blood samples that were collected at Week 7 or Week 13 and the patient must have been randomized to the everolimus arm and be receiving protocol treatment at the time of the blood draw. At the time of the on-study analysis in the winter of 2014, there were 83 patients with one blood draw and 165 with two for a total of 248 patients. For those with two on-treatment measurements, the average of the two will be used for analysis to reduce measurement error bias.

The purpose of the analysis is to correlate everolimus blood concentrations from early blood draws with the experience of adverse events by the patients, both in terms of general grades of toxicities but also by specific adverse events that have been more frequently reported on the everolimus arm. The following calculations assume a PK analysis will be conducted prior to accrual completion in order to gain insight into the relationship between blood levels of the study drug and adverse events. We anticipate there will be more samples to evaluate later in the trial and so effect sizes will be smaller with larger sample sizes.

#### Most Prevalent Grade 2-4 Adverse Events in the Everolimus Arm of EVEREST

Among all Randomized Patients on the Everolimus Arm Who Received Any Study Drug

Toxicity	% of Evaluable with Grade 2-4
High Cholesterol	10%
Fatigue	19%
Hyperglycemia	14%
Hypertriglyceridemia	27%
Oral mucositis	35%
Rash	14%
<b>Composite Endpoints</b>	
Any Toxicity Grade 2-4	87%
Any Toxicity Grade 3-4	46%
Refusal/Tox within first 3 months	25%
Refusal/Tox within first 6 months	41%
Refusal/Tox prior to 12 months	52%

In order to simplify power calculations related to everolimus blood concentrations, we will assume the distribution of values will be divided into quartiles. The following table indicates the minimally detectable odds ratio that could be detected between the lowest and highest quartile in terms of predicting an adverse event. A range of prevalences are illustrated below to show how the effect size changes with the prevalence of the adverse event.

Minimally Detectable Odds Ratio for Highest versus Lowest Quartile of everolimus in the blood, assuming 80% Statistical Power and a Two-sided Alpha=0.05.

	Prevalence of Adverse Event Endpoint				
	10%	20%	30%	40%	50%



Q4 vs. Q1 of everolimus concentration	6.5	3.6	3.0	2.7	2.7
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An individual adverse event that is only reported by 10% of patients who receive everolimus will need to have a very strong association with concentration of everolimus in the blood (odds ratio 6.5 between highest and lowest concentration) in order to be detected as a significant association. An association of any Grade 3-4 toxicity only needs to be in the range of an odds ratio of 2.7 to be detectable.

For patients who have had a dose reduction of protocol therapy at the time of their blood draw, we will handle this in two ways. First, we will just analyze the everolimus level as it appears in the blood and ignore the dose received, and the second approach will standardize the amount of everolimus in the blood conditional on the dose of drug taken.

Logistic regression will be used to model adverse event outcomes with everolimus blood concentration as a predictor, adjusting for other stratification factors and age, gender and race.

#### 11.6 Data and Safety Monitoring Committee Oversight

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

### 12.0 DISCIPLINE REVIEW

There will be no formal discipline review done in conjunction with this study.

### 13.0 REGISTRATION GUIDELINES

#### 13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment).

#### 13.2 Investigator/Site Requirements

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site ([http://ctep.cancer.gov/investigatorResources/investigator\\_registration.htm](http://ctep.cancer.gov/investigatorResources/investigator_registration.htm)). Questions should be directed to the CTEP Investigator Registration Help Desk by e-mail at [pmbregpend@ctep.nci.nih.gov](mailto:pmbregpend@ctep.nci.nih.gov).



Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at <https://www.ctsu.org>.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

### 13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

- a. Institution CTEP ID
- b. Protocol Number
- c. Registration Step
- d. Treating Investigator
- e. Cooperative Group Credit
- f. Credit Investigator
- g. Patient Initials
- h. Patient's Date of Birth
- i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- j. Country of Residence
- k. ZIP Code
- l. Gender (select one):
  - Female Gender
  - Male Gender



- m. Ethnicity (select one):
- Hispanic or Latino
  - Not Hispanic or Latino
  - Unknown
- n. Method of Payment (select one):
- Private Insurance
  - Medicare
  - Medicare and Private Insurance
  - Medicaid
  - Medicaid and Medicare
  - Military or Veterans Sponsored NOS
  - Military Sponsored (Including Champus & Tricare)
  - Veterans Sponsored
  - Self Pay (No Insurance)
  - No Means of Payment (No Insurance)
  - Other
  - Unknown
- o. Race (select all that apply):
- American Indian or Alaska Native
  - Asian
  - Black or African American
  - Native Hawaiian or other Pacific Islander
  - White
  - Unknown

#### 13.4 Registration Procedures

- a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application that is integrated with the CTSU Enterprise System for regulatory and roster data and, at the time of patient registration, initializes the patient in the Rave database. OPEN can be accessed at <https://open.ctsu.org> or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>, or from the OPEN Patient Registration link on the SWOG CRA Workbench.
- b. Prior to accessing OPEN site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to [Section 5.0](#) to verify eligibility.
  - All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
  - The study site is listed as "approved" in the CTSU RSS.
- c. Access requirements for OPEN:
- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at





[http://ctep.cancer.gov/branches/pmb/associate\\_registration.htm](http://ctep.cancer.gov/branches/pmb/associate_registration.htm).  
Questions should be directed to the CTEP Associate Registration Help Desk by e-mail at [ctepreghelp@ctep.nci.nih.gov](mailto:ctepreghelp@ctep.nci.nih.gov).

- To perform registrations, the site must have been assigned the 'Registrar' role on the SWOG or CTSU roster:
  1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.
  2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or [ctsucontact@westat.com](mailto:ctsucontact@westat.com).





- 13.5 Exceptions to SWOG registration policies will not be permitted.
- a. Patients must meet all eligibility requirements.
  - b. Institutions must be identified as approved for registration.
  - c. Registrations may not be cancelled.
  - d. Late registrations (after initiation of treatment) will not be accepted.

## 14.0 DATA SUBMISSION SCHEDULE

### 14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

### 14.2 Master Forms

Master forms are included in [Section 18.0](#) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see [Section 14.3a](#) for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

### 14.3 Data Submission Procedures

- a. SWOG institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (<http://swog.org>) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the [swog.org](http://swog.org) Members logon page). For other difficulties with the CRA Workbench, please email [technicalquestion@crab.org](mailto:technicalquestion@crab.org).

- b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may



submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

- c. Data Submission Instructions for non-SWOG Institutions (CTSU): See the [CTSU participation table](#).

#### 14.4 Data Submission Overview and Timepoints

- a. WITHIN 7 DAYS OF REGISTRATION:

Submit copies of the following:

**S0931** Prestudy Form

**S0931** Tumor Specimen Processing Form (for patients who consent to the translational medicine studies)

Surgical and Radiology Reports

Pathology Report confirming renal cell carcinoma including subtypes.

- b. IF PATIENT CONSENTED:

Submit specimens within 28 days of obtaining as outlined in [Section 15.0](#).

- c. WITHIN 7 DAYS OF COMPLETION OF EACH CYCLE (EVERY SIX WEEKS) WHILE ON PROTOCOL TREATMENT:

**S0931** Treatment Form

**S0931** Adverse Event Form

- d. EVERY EIGHTEEN WEEKS FOR THE FIRST 54 WEEKS (REGARDLESS OF EARLY PROTOCOL TREATMENT DISCONTINUATION), AND THEN EVERY 6 MONTHS FOR THE FOLLOWING 2 YEARS, AND THEN ANNUALLY UNTIL 10 YEARS AFTER REGISTRATION, RECURRENCE OR DEATH WHICHEVER COMES FIRST:

**S0931** Recurrence Assessment Form

- e. WITHIN 14 DAYS OF DISCONTINUATION OF ALL PROTOCOL TREATMENT:

Off Treatment Notice

Final **S0931** Treatment Form

Final **S0931** Adverse Event Form

- f. AFTER OFF ALL PROTOCOL TREATMENT, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY UNTIL TEN YEARS AFTER REGISTRATION OR UNTIL DEATH:

Submit copies of the **S0931** Specific Follow Up Form



- g. WITHIN 14 DAYS OF RECURRENCE:
- S0931** Adverse Event Form
- Off Treatment Notice
- If patient was off protocol treatment:
- S0931** Specific Follow-Up Form
- For all patients:
- S0931** Recurrence Assessment Form
- Radiology and pathology reports documenting recurrence.
- h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:
- If patient was still on protocol treatment:
- Notice of Death
- Final S0931** Treatment Form
- Final S0931** Adverse Event Form
- If patient was off protocol treatment:
- Notice of Death
- S0931** Specific Follow-Up Form

## 15.0 SPECIAL INSTRUCTIONS

### 15.1 Tissue Specimen Banking

Tissue specimens for banking and future translational medicine studies will be submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201. Specimen banking is optional for the patient.

- a. With patient's consent tissue specimens must be submitted at the timepoint listed below in [Section 15.1b](#) (see [Section 9.0](#)):
- b. A paraffin embedded block of tumor or 10 unstained slides obtained from the prestudy nephrectomy specimen must be submitted to Lab #201 within 7 days of registration. This specimen will be banked until funding is obtained to perform translational medicine studies which will include assessing molecular biomarkers relevant to the AKT/mTOR and other pathways implicated in the pathogenesis of renal carcinoma and investigating their potential predictive and prognostic value.
- Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>), or via the link on the **S0931** protocol abstract page on the SWOG website ([www.swog.org](http://www.swog.org)).
- c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.



## 15.2 Plasma, Buffy Coat, and Whole Blood Specimen Banking

Plasma, buffy coat and whole blood specimens for banking and future translational medicine studies will be submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201. Specimen banking is optional for the patient.

a. With patient's consent plasma and buffy coat and whole blood specimens must be submitted at the timepoints listed below in [Section 15.2b](#). Collection instructions are outlined in [Section 15.2c](#) and submission instructions are outlined in [Section 15.2e](#).

b. With patient's consent plasma and whole blood specimens must be submitted at the following times (see [Section 9.0](#)):

### 1. Plasma and Buffy Coat

Blood specimens (two purple top EDTA tubes for plasma and buffy coats) will be collected after registration, but prior to Cycle 1 treatment; at the beginning of Cycles 2 and 3; at the time of removal from protocol treatment (regardless of timepoint); and at the time of disease recurrence. These specimens must be shipped within 28 days after obtaining to Lab #201. These specimens will be banked until funding is obtained to perform translational medicine studies which will include assessing molecular biomarkers relevant to the AKT/mTOR and other pathways implicated in the pathogenesis of renal carcinoma and investigating their potential predictive and prognostic value.

### 2. Whole Blood

Five mL of venous blood will be collected in a purple-top EDTA tube immediately prior to Cycles 1-3 and at the time the patient is removed from protocol treatment. **Prior to Cycles 1-3, patients must be instructed not to take their morning everolimus dose until after the samples have been obtained.** These specimens must be shipped within 28 days after obtaining to Lab #201. These specimens will be banked until funding is obtained to perform translational medicine studies which will include determining the steady-state everolimus trough levels.

c. Plasma and Whole Blood Specimen Collection Instructions:

### 1. Plasma and Buffy Coat Specimen Collection and Processing Instructions:

a. Blood samples should be collected using standard venipuncture technique.

b. Cryovials must be labeled with the protocol number (**S0931**), SWOG patient number, patient's initials, and date and time of specimen collection.

c. Collect ~6 mL whole blood in each of two (2) purple top tubes (EDTA tubes).



- d. Immediately invert tube (gently) 8-10 times. This reduces the possibility of clot formation.
  - e. Centrifuge sample at 800 x g for 10 minutes (~1500-2000 rpm, determined by centrifuge rotor size).
  - f. Immediately after centrifuging, transfer plasma in 1 mL aliquots to labeled cryovials.
  - g. Pipette slowly to avoid disturbing the buffy coat layer.
  - h. Leave a small amount of plasma (~.5 cm) above the buffy coat layer in each tube.
  - i. After removing plasma from both tubes, transfer buffy coat to labeled cryovials.
    - The buffy layer is the off-white layer between the plasma and the red blood cells.
    - Pipette slowly in a circular motion to obtain as many buffy coat cells as possible.
    - Contamination of the buffy coat with red blood cells is expected and not a concern.
  - j. Immediately freeze vials in a freezing apparatus (ex. Mr. Frosty). If not available, slow freeze vials on dry ice or in a -70°C freezer. Store frozen plasma vials in a -70°C to -80°C freezer until ready to ship. If a -70°C to -80°C freezer is not available, a -20°C would be sufficient.
2. Whole Blood Specimen Collection Instructions:
- a. Prior to each scheduled appointment, patients must be instructed not to take their morning everolimus dose until after the sample has been obtained.
  - b. Blood samples should be collected using standard venipuncture technique.
  - c. Cryovials must be labeled with the protocol number (**S0931**), SWOG patient number, patient's initials, and date and time of specimen collection.
  - d. Collect 5 mL of venous blood into a purple top EDTA tubes.
  - e. Immediately invert tube (gently) 8-10 times. This reduces the possibility of clot formation.
  - f. If you are using plastic vacutainer tubes, samples can be directly frozen at -20°C. If the blood collection tubes are glass, whole blood should be transferred to an appropriately labeled polypropylene freezer vial and frozen at <-20°C. **Note: Plasma should not be separated from whole blood. Whole blood should be frozen directly without separation.**
- d. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.



e. SHIPPING SAMPLES

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (<http://swog.org>) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at <https://gill.crab.org/SpecTrack/>.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to [technicalquestion@crab.org](mailto:technicalquestion@crab.org). For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page

(<http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf>); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of plasma, whole blood and tissue specimens for SWOG Repository submission is identified as follows:

Lab #201: SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division  
Contact: Erin Grundy  
Phone: 614/355-3099  
Email: [bpccbank@nationwidechildrens.org](mailto:bpccbank@nationwidechildrens.org)

2. Plasma, buffy coats, and whole blood must be shipped on dry ice by overnight courier Monday through Wednesday.

3. Federal guidelines for the shipment of blood products:

- a. The tube must be wrapped in an absorbent material.
- b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).
- c. Pack the resealable bag and tube in a Styrofoam shipping container.



- d. Pack the Styrofoam shipping container in a cardboard box.
- e. Mark the box "Biohazard".

## 16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

### Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

### Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

### Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

### Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

### Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

#### 16.1 Adverse Event Reporting Requirements

##### a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in [Section 14.0](#).) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

##### b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A



CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at:  
[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/adverse\\_events.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to [Table 16.1](#)) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at [adr@swog.org](mailto:adr@swog.org). Once Internet connectivity is restored, a 24-hour notification that was made by phone or using [adr@swog.org](mailto:adr@swog.org) must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in [Table 16.1](#).

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in [Table 16.1](#). The investigational agent used in this study is everolimus. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the SWOG Operations Office, 210-614-8808 or [adr@swog.org](mailto:adr@swog.org), before preparing the report.





**Table 16.1:**

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on studies under a Non-CTEP IND within 30 Days<sup>1</sup> of the Last Administration of the Investigational Agent/Intervention<sup>1</sup> (Everolimus).**

<p><b>FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)</b>  <b>NOTE:</b> Investigators <b>MUST</b> immediately report to the sponsor (NCI) <b>ANY</b> Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)</p> <p>An adverse event is considered serious if it results in <b>ANY</b> of the following outcomes:</p> <ol style="list-style-type: none"> <li>1) Death</li> <li>2) A life-threatening adverse event</li> <li>3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for <math>\geq</math> 24 hours</li> <li>4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions</li> <li>5) A congenital anomaly/birth defect.</li> <li>6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).</li> </ol>				
<p><b>ALL SERIOUS</b> adverse events that meet the above criteria <b>MUST</b> be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.</p>				
Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization $\geq$ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization $\geq$ 24 hrs	Not required	10 Calendar Days		
<p><b>NOTE:</b> Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [<a href="#">Section 16.1f.</a>]</p> <p><b>Expedited AE reporting timelines are defined as:</b></p> <ul style="list-style-type: none"> <li>o “24-Hour; 5 Calendar Days” - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.</li> <li>o “10 Calendar Days” - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.</li> </ul>				
<p><sup>1</sup>Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:</p> <p><b>Expedited 24-hour notification followed by complete report within 5 calendar days for:</b></p> <ul style="list-style-type: none"> <li>• All Grade 4, and Grade 5 AEs</li> </ul> <p><b>Expedited 10 calendar day reports for:</b></p> <ul style="list-style-type: none"> <li>• Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization</li> <li>• Grade 3 adverse events</li> </ul>				
<p><b>May 5, 2011</b></p>				



f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Trials Utilizing an Agent under a Non-CTEP IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2) The adverse event listed below does not require expedited reporting via CTEP-AERS:

- Grade 4 myelosuppression

g. **Reporting of Secondary Malignancy Including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

*Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.*

For more information see:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/aeguidelines.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf).

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210/614-0006 or mail to the address below:



- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG  
ATTN: SAE Program  
4201 Medical Drive, Suite 250  
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. Reporting Pregnancy, Fetal Death, and Death Neonatal

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 “Pregnancy, puerperium and perinatal conditions – Other (pregnancy)”** under the **Pregnancy, puerperium and perinatal conditions SOC**.

*Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.*

2. **Fetal Death** Fetal Death defined in CTCAE as “A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation” should be reported expeditiously as **Grade 4 “pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)”** under the **Pregnancy, puerperium and perinatal conditions SOC**.

3. **Death Neonatal** Neonatal death, defined in CTCAE as “A disorder characterized by cessation of life occurring during the first 28 days of life” that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 “General disorders and administration – Other (neonatal loss)”** under the **General disorders and administration SOC**.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

**NOTE:** When submitting CTEP-AERS reports for “Pregnancy, “Pregnancy loss”, or “Neonatal loss”, the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301/230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the “Description of Event” section of the CTEP-AERS report.

The Pregnancy Information Form is available at:  
[http://ctep.cancer.gov/protocolDevelopment/adverse\\_effects.htm](http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm)



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**18.0 APPENDIX**

- 18.1 New York Heart Association Classifications
- 18.2 Emergency Unblinding Guidelines
- 18.3 Examples of Clinically Relevant Drug Interactions: Substrates, Inducers and Inhibitors of the Isoenzyme CYP3A4
- 18.4 Intake Calendar



18.1 New York Heart Association Classifications

TABLE I, NEW YORK HEART ASSOCIATION CLASS

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

\* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

\*\* At accustomed occupation or usual tasks.





## 18.2 Emergency Unblinding Guidelines

### a. **General Considerations**

The randomized regimen for this study includes a blinded drug, which is either everolimus or placebo. During the course of this study it may become necessary to identify (or unblind) a patient's treatment assignment. The circumstances that will warrant emergency unblinding and the procedure for emergency unblinding are described in this Appendix.

PLEASE NOTE: Unblinding requests for disease recurrence **MUST** be handled by the planned unblinding instructions outlined in [Section 7.5](#). Do not contact the Washington Poison Center with these requests.

### b. **Criteria for Emergency Unblinding**

In general, treatment assignments will not be emergency unblinded unless there is a compelling medical or ethical reason that the treatment should be identified. In most circumstances it will be appropriate to treat the patient or person who received blinded drug as though he or she received everolimus, irrespective of the drug actually received. Therefore, emergency unblinding should seldom be necessary.

The following events **MAY** require emergency unblinding of treatment assignments in this study:

1. A compelling medical need as determined by a physician, e.g., existence of a condition for which knowledge of the patient's treatment assignment is necessary for the selection of appropriate care.
2. Administration of blinded drug to a person other than the patient.

### c. **Procedure for Emergency Unblinding**

Emergency unblinding of treatment assignments for patients on this study will be performed by the Washington Poison Center (WPC), upon approval from a designated physician (either one of the WPC's resource physicians or Dr. Christopher Ryan). The procedure for emergency unblinding the treatment assignment for a patient on this study is as follows:

1. All requests for emergency unblinding must be made by the registering physician or his/her designee.
2. Call the WPC collect at 206/526-2121 from outside Washington State or toll free at 800/222-1222 from within Washington State. The WPC is accessible 24 hours per day, 365 days per year.
3. The person calling the WPC must be prepared to provide the following information:

Study number (**S0931**)

SWOG Patient Number (e.g., "999999")

Patient Initials

Name and telephone number of the caller

Reason emergency unblinding is thought to be required



4. The WPC will contact one of its resource physicians and provide the information received from the caller. If none of the WPC's resource physicians can be contacted, then the WPC will contact Dr. Christopher Ryan. The contacted physician will evaluate the need for emergency unblinding and provide the WPC either approval to unblind or a recommendation for treatment, if any, while maintaining blinding. The WPC will then call the person who initiated the unblinding request and tell him/her either the treatment assignment or the resource physician's treatment recommendation.
5. If the WPC is unable to contact any of its resource physicians or Dr. Ryan within three hours after receiving the request for emergency unblinding, then the WPC will notify the person who initiated the unblinding request that treatment assignment will not be unblinded at that time and treatment of the patient or person who received blinded drug should proceed as if the blinded drug is everolimus. In such cases, the WPC will continue to attempt to contact the resource physicians, and when one of them is contacted, will proceed as in #4 above.
6. Any patient whose treatment assignment is emergency unblinded will receive no further blinded drug, but should continue all other protocol treatment if his/her medical condition permits.
7. Unblinding of treatment assignments for any reason must be documented on the Off Treatment Notice.

Questions regarding the unblinding may be directed to any of the following resource physicians:

Christopher W. Ryan, M.D.  
Oregon Health & Science University  
3303 SW Bond Avenue, CH14R  
Portland, OR 97239  
Phone: 503/494-8487

Bruce G. Redman, D.O.  
SWOG  
24 Frank Lloyd Wright Drive  
P.O. Box 483  
Ann Arbor, MI 48106  
Phone: 734/998-7154

Washington Poison Center  
Phone: 206/526-2121



18.3 Examples of Clinically Relevant Drug Interactions: Substrates, Inducers and Inhibitors of the Isoenzyme CYP3A4

Only the strong CYP3A4 inducers and inhibitors listed in [Section 5.2e](#) are prohibited during study treatment. Refer to [Sections 7.1c](#) and [7.3](#) for guidance regarding the use of moderate CYP3A4 inducers and inhibitors while on treatment.

**CYP3A4 Substrates**

Albuterol	Dihydroergotamine	Isradipine	Quinidine
Alfentanil	Diltiazem	Itraconazole	Rabeprazole
Alprazolam	Disopyramide	Ketamine	Ranolazine
Amiodarone	Docetaxel	Ketoconazole	Repaglinide
Amlodipine	Doxepin	Lansoprazole	Rifabutin
Amprenavir	Doxorubicin	Letrozole	Ritonavir
Aprepitant	Doxycycline	Levonorgestrel	Salmeterol
Aripiprazole	Efavirenz	Lidocaine	Saquinavir
Atazanavir	Eletriptan	Losartan	Sibutramine
Atorvastatin	Enalapril	Lovastatin	Sildenafil
Benzphetamine	Eplerenone	Medroxyprogesterone	Simvastatin
Bisoprolol	Ergoloid mesylates	Mefloquine	Sirolimus
Bortezomib	Ergonovine	Mestranol	Spiramycin
Bosentan	Ergotamine	Methadone	Sufentanil
Bromazepam	Erythromycin	Methylergonovine	Sunitinib
Bromocriptine	Escitalopram	Methysergide	Tacrolimus
Budesonide	Estradiol	Miconazole	Tamoxifen
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamsulosin
Buspirone	Estrogens, conj., equine	Miglustat	Telithromycin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Teniposide
Carbamazepine	Estrone	Modafinil	Tetracycline
Cerivastatin	Estropipate	Montelukast	Theophylline
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tiagabine
Chloroquine	Ethosuximide	Nateglinide	Ticlopidine
Chlorpheniramine	Etoposide	Nefazodone	Tipranavir
Cilostazol	Exemestane	Nelfinavir	Tolterodine
Cisapride	Felbamate	Nevirapine	Toremifene
Citalopram	Felodipine	Nicardipine	Trazodone
Clarithromycin	Fentanyl	Nifedipine	Triazolam
Clobazam	Flurazepam	Nimodipine	Trimethoprim
Clonazepam	Flutamide	Nisoldipine	Trimipramine
Clorazepate	Fluticasone	Norethindrone	Troleandomycin
Cocaine	Fosamprenavir	Norgestrel	Vardenafil
Colchicine	Gefitinib	Ondansetron	Venlafaxine
Conivaptan	Haloperidol	Paclitaxel	Verapamil
Cyclophosphamide	Ifosfamide	Pergolide	Vinblastine
Cyclosporine	Imatinib	Phencyclidine	Vincristine
Dantrolene	Indinavir	Pimozide	Vinorelbine
Dapsone	Irinotecan	Pipotiazine	Zolpidem
Dasatinib (1)	Isosorbide	Primaquine	Zonisamide
Delavirdine	Isosorbide dinitrate	Progesterone	Zopiclone
Diazepam	Isosorbide mononitrate	Quetiapine	

**CYP3A4 Inhibitors**

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranlycypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

### CYP3A4 Inducers

Aminoglutethimide Carbamazepine Fosphenytoin Nafcillin	Nevirapine Oxcarbazepine Pentobarbital Phenobarbital	Phenytoin Primidone Rifabutin Rifampin	Rifapentine St. John's wort (3)
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When drugs classified as 'substrates' are co-administered with everolimus, there is the potential for higher concentrations of the 'substrate'. When everolimus is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of everolimus is the potential outcome. The co-administration of 'inducers' would potentially lower plasma everolimus concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed. Additional information for drug interactions with cytochrome P450 isoenzymes can be found at <http://medicine.iupui.edu/flockhart/>.

### PgP Inhibitors

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole, ketoconazole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valsopodar, verapamil	rifampin, St John's wort

18.4 Intake Calendar

<b>SWOG Patient ID</b> _____ <b>Patient Initials (L, F, M)</b> _____ <b>SWOG Study #</b> _____ <b>Institution/Affiliate</b> _____ <b>Physician</b> _____
<p><b>Instructions for the participant:</b>  This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.</p> <p>If you have questions contact: _____ Telephone: _____</p> <p>Your next appointment is: _____</p>
<p><b>Special instructions:</b></p>  
<p><b>Month:</b> _____ <b>Year:</b> _____</p>

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: \_\_\_\_\_



## Informed Consent Model for S0931

### **\*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:**

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making additions, deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

**Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.**

Readability Statistics:
Flesch Reading Ease <u>64.7</u> (targeted above 55)
Flesch-Kincaid Grade Level <u>8.0</u> (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

SWOG must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.



- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

\*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, \_\_\_\_\_, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs> or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

\*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.





## **S0931, "EVEREST: EVERolimus for Renal Cancer Ensuing Surgical Therapy, a Phase III Study"**

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have cancer of the kidney that has been surgically removed.

### **Why is this study being done?**

**The purpose of this study is to see whether treatment with everolimus after surgery for kidney cancer will increase the time without cancer returning. The current standard treatment after surgery is careful monitoring with no immediate treatment. Studies suggest that one way kidney cancer may grow is through chemical signaling through a protein named "mTOR". Everolimus is a drug that stops signaling through mTOR and may therefore stop the growth of kidney cancer. Everolimus is a drug currently approved for the treatment of patients with advanced or metastatic kidney cancer. It is considered investigational for use after surgery. In this study, you will get either everolimus or placebo (a pill with no medication). You will not get both.**

### **How many people will take part in the study?**

About 1,537 people will take part in this study.

### **What will happen if I take part in this research study?**

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history including screening for hepatitis B and C risk and physical examination,
- Blood tests for blood counts and to test your kidney and liver function,
- Blood tests to check your blood sugar (glucose) and lipids (cholesterol and triglycerides),
- CT scan to assess your disease.

During the study ... *(section updated 5/6/14)*

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.



- History and physical exam at the beginning of Week 1 and Week 4. (NOTE: If you receive a prestudy history and physical exam within 28 days prior to starting on this study, then these tests do not need to be repeated during Week 1.)
- Physical exam at the beginning of each 6 week cycle (Week 7, 13, 19, etc.) for a maximum of 9 cycles, (2/11/16)
- Blood tests for blood counts and to test your kidney and liver function at the beginning of each 6 week cycle (Week 7, 13, 19, etc.) for a maximum of 9 cycles, (2/11/16)
- Blood tests to check your blood sugar (glucose) and lipids (cholesterol and triglycerides) at the beginning of each 6 week cycle (Week 7, 13, 19, etc.) for a maximum of 9 cycles, (2/11/16)
- CT scan to assess your disease every eighteen weeks.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin except that a computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. Once you have been placed into one of the groups, neither you nor your doctor will know which group you are in. The treatment in each group will be identical except that half of the patients will receive the investigational drug everolimus and half will take an identical placebo pill. Placebo pills do not contain any medication. These pills will look just like the pills containing everolimus. (5/6/14)

You will take two pills once a day by mouth with a glass of water and no more than a light fat-free meal. (7/11/12) Tablets must be swallowed whole and not chewed or crushed. Due to interaction with everolimus, you must not consume grapefruit or grapefruit juice while on study.

You will record the number of pills you take each day and any side effects you experience on a calendar. For the first 6 weeks, your doctor's office will call you to see how you are doing on the weeks that you don't have visits scheduled. You should bring your calendar with you each time you have a doctor's visit. During your visits, your pills will be counted and your calendar reviewed. For this study, each six-week treatment period is called a cycle. Treatment will continue for nine cycles (54 weeks) as long as you are able to tolerate treatment and your cancer hasn't returned. All treatment can be given without being admitted to a hospital.

If your cancer returns, your treatment may be unblinded by your doctor to find out if you were receiving everolimus or placebo. Your doctor may want this information to decide on additional treatment options for you. You or your insurance company will be responsible for the cost of treatment with everolimus if and when your doctor prescribes it for you off study. (*paragraph added 7/11/12*)

## **How long will I be in the study?**

You will be asked to take the study drug for nine six-week cycles, or until your side effects become too great, or until your cancer returns. While you are receiving study treatment, you will



need to come to the clinic for doctor visits every six weeks for the first 54 weeks including visits for scans every 18 weeks (or every 4 months). (12/15/14) After you are finished with the study treatment, you will return to the clinic with scans every six months for Years 2 and 3, and then yearly thereafter until 10 years after registration. (12/15/14)

### **Can I stop being in the study?**

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. It is important to tell the study doctor if you are thinking about stopping so any risks from the study drug can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

### **What side effects or risks can I expect from being in the study?**

**You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.**

**You should talk to your study doctor about any side effects that you have while taking part in the study.**

*Risks and side effects related to everolimus/placebo include those which are: (section updated 12/15/14, 5/6/14, 2/11/16, updated 6/6/16, 11/11/16) (10/3/17)*

<b>COMMON, SOME MAY BE SERIOUS</b>
In 100 people receiving Everolimus/Placebo, more than 20 and up to 100 may have:
<ul style="list-style-type: none"><li>● <b>Anemia which may require blood transfusion</b></li><li>● <b>Diarrhea</b></li><li>● <b>Sores in the mouth which may cause difficulty swallowing</b></li><li>● <b>Tiredness</b></li><li>● <b>Rash</b></li></ul>



**OCCASIONAL, SOME MAY BE SERIOUS**

In 100 people receiving everolimus, from 4 to 20 may have:

- **Pain**
- **Constipation, nausea, vomiting**
- **Swelling of the arms, legs**
- **Fever**
- **Infection, especially when white blood cell count is low**
- **Bruising, bleeding**
- **Weight loss, loss of appetite**
- **Changes in taste**
- **Headache**
- **Cough, shortness of breath**
- **Nose bleed**
- **Damage to the lungs which may cause shortness of breath**
- **Dry skin**
- **Itching**

**RARE, AND SERIOUS**

In 100 people receiving everolimus, 3 or fewer may have:

- **Non-healing surgical site**
- **Kidney damage which may require dialysis**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**

**Reproductive risks:** You should not become pregnant or father a baby while on this study and for at least 8 weeks following completion of therapy because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study and for at least 8 weeks following completion of therapy. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

The study drug may interact with other medications. Cases of a type of pneumonia (caused by a fungus called *Pneumocystis jirovecii*), some with a fatal outcome, have been reported in patients who received everolimus. This type of pneumonia has been linked to the use of corticosteroids or other drugs that can weaken the immune system while using everolimus. Patients taking angiotensin converting enzyme (ACE) inhibitor therapy may be at an increased risk for swelling of the airways or tongue, with or without damage to the lungs. You should tell your study doctor about all medications (over the counter, herbal, and prescription) you are currently taking and check with your study doctor before beginning any new medications. *(Paragraph updated 12/15/14)*



**Vaccines help protect people from certain illnesses. There is a chance that receiving everolimus could interfere with any vaccinations you receive. Some vaccines are made from live bacteria or live viruses. You cannot receive this kind of vaccine (for example FluMist™ or BCG) for seven days prior to going on study or during the study.**

**For more information about risks and side effects, ask your study doctor.**

### **Are there benefits to taking part in the study?**

**Taking part in this study may or may not make your health better. While doctors hope the study drug will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about everolimus as a treatment for cancer. This information could help future cancer patients.**

### **What other choices do I have if I do not take part in this study?**

**Your other choices may include:**

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

**Talk to your doctor about your choices before you decide if you will take part in this study.**

### **Will my medical information be kept private?**

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- SWOG
- Qualified representative from Novartis Pharmaceuticals (manufacturer of everolimus)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. (12/15/14) This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. (12/15/14) You can search this Web site at any time. (paragraph added 7/11/12)



*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

## **What are the costs of taking part in this study?**

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drug will be *(provided free of charge/charged in the usual way)*. The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate)*. *(local institutions must choose the option that best fits the hospital's situation)*

Novartis Pharmaceuticals will supply the investigational agent everolimus or placebo at no charge while you take part in this study. Novartis Pharmaceuticals does not cover the cost of getting the everolimus or placebo ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that Novartis Pharmaceuticals may not continue to provide the everolimus or placebo for some reason. If this would occur, other possible options are:

1. You might be able to get the everolimus from your pharmacy but you or your insurance company may have to pay for it.
2. If there is no everolimus or placebo available at all, no one will be able to get more and the study would close.

If a problem with getting everolimus or placebo occurs, your study doctor will talk to you about these options. *(paragraph added 7/11/12)*

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/about-cancer/treatment/clinical-trials/paying/insurance>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site. *(revised 2/11/16)*

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.



## **What happens if I am injured because I took part in this study?**

It is important that you tell your study doctor, \_\_\_\_\_ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at \_\_\_\_\_ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

## **What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

## **Who can answer my questions about the study?**

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor \_\_\_\_\_ *[name(s)]* at \_\_\_\_\_ *[telephone number]*.

**For questions about your rights while taking part in this study, call the \_\_\_\_\_ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at \_\_\_\_\_ *(telephone number)*. *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]***

\*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[\*Only applies to sites using the CIRB.]*

*(paragraph deleted 7/11/12)*





Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

*(paragraph deleted 7/11/12)*

### **Future Contact**

**I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.**

Yes                      No

## **Consent Form for Use of Specimens for Research**

### About Using Specimens for Research

We would like to keep some specimens for future research. *(7/11/12)* If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research. *(paragraph moved up 7/11/12)*

If you agree, a sample of your blood and tumor tissue will be banked for future research to study the biology of your cancer and how everolimus works. *(7/11/12)* The blood samples will be obtained to measure the level of everolimus in your blood. We will see if those levels correspond to the risk of getting certain side effects. In the tumor samples we will measure the levels of certain proteins to see if they predict how well everolimus will work. The blood sample (about 3 ½ teaspoons) will be collected before you begin study treatment, before Cycles 2 and 3, when you go off protocol treatment, and if your cancer recurs. The blood sample must be taken before your daily dose of study drug. The tumor tissue sample will be taken from your kidney cancer specimen (obtained from your recent operation). (You will not need to have another surgery for this purpose.) These collections are optional. *(sentences deleted 7/11/12)*

*(section deleted 7/11/12)*

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

### Things to Think About





The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While SWOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance. *(paragraph added 7/11/12)*

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it. *(paragraph added 7/11/12)*

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

## Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.



## Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

## Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

- 1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**  
Yes                      No
- 2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**  
Yes                      No
- 3. Someone may contact me in the future to ask me to allow other uses of my specimens.**  
Yes                      No

**If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.**

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) *(revised 2/11/16)*

You may also visit the NCI Web site at <http://cancer.gov/>



- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

## Signature

I have been given a copy of all \_\_\_\_\_ [*insert total of number of pages*] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant \_\_\_\_\_

Date \_\_\_\_\_



## **Specimen Consent Supplemental Sheets**

### **How are Specimens Used for Research?**

#### **Where do specimens come from?**

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

#### **Why do people do research with specimens?**

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

#### **What type of research will be done with my specimen?**

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

#### **How do researchers get the specimen?**

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

#### **Will I find out the results of the research using my specimen?**

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

#### **Why do you need information from my health records?**

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

#### **Will my name be attached to the records that are given to the researcher?**

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.



**How could the records be used in ways that might be harmful to me?**

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

**How am I protected?**

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

**What if I have more questions?**

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

