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Phase II Study of Everolimus (RAD001) in Metastatic Transitional Cell Carcinoma of the Urothelium

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open-label Phase II study of Everolimus (RAD001) in patients with progressive advanced/metastatic urothelial carcinoma that have progressed despite treatment with prior cytotoxic chemotherapy. The primary objective of the study is to measure the 2-month PFS rate of Everolimus (RAD001) as determined by RECIST. Everolimus will be administered at a dose of 10 mg orally once daily continuously. Intra-patient dose reduction may be required depending on the type and severity of the individual toxicity encountered. Re-staging imaging studies will be performed after every two cycles of treatment (one cycle = 4 weeks) during the first five years of treatment, and after every 3-6 cycles of treatment thereafter. Patients may continue on study as long as they are tolerating therapy and are free of disease progression.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary

- To measure PFS of Everolimus (RAD001) as determined by RECIST
- To determine the safety and toxicity of Everolimus (RAD001) in this patient population.

Secondary

- To determine the response rate of Everolimus (RAD001) in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy
- To assess markers for activated mTOR pathway (including phospho-S6 and phsopho-4E BP1) in all pre-treatment specimens and correlate with response to treatment and PFS.

3.1 BACKGROUND AND RATIONALE

3.2 Urothelial Cancer

In the United States, urothelial carcinoma (UC) of the bladder is the fourth most common malignancy in men and the ninth most common in women with an estimated 67,160 new cases (50,040 men and 17,120 women) and 13,750 deaths (9,630 men and 4,120 women) for the year 2007[1]. Although UC is a chemosensitive malignancy with response proportions of over 50% with conventional cytotoxic regimens, the response durations are short and the median survival of patients with metastatic disease is approximately 14 months [2]. Second-line trials with cytotoxic agents have generally yielded discouraging response rates (see table below) with a median progression-free survival between 2 to 3 months and a median survival in the range of 6 to 9 months[3-6]. Furthermore, many patients receive these agents as part of first-line therapy leaving few available options for patients with progressive or recurrent disease. There is no FDA-approved drug for this setting and no standard conventional chemotherapy agent(s) have demonstrated a survival benefit in patients with metastatic urothelial cancer that has progressed after first line platinum-based chemotherapy. This highlights the need for the development of

novel therapies for the treatment of patients with metastatic UC.

Table 1. Results with cytotoxic agents in patients with metastatic urothelial carcinoma who had received prior chemotherapy

Agent	Activity	
	Overall Response	95% CI
Paclitaxel[4, 7, 8]	9%	0-17%
Docetaxel[3, 9]	13%	4-30%
Ifosfamide[10-12]	20%	10-32%
Gemcitabine[13, 14]	23%	8-38%

3.3 Rationale for Everolimus in Urothelial Carcinoma

At Memorial Sloan-Kettering Cancer Center (MSKCC), we performed an immunohistochemical (IHC) study to assess whether mTOR pathway markers are expressed in high-stage bladder urothelial carcinomas. The study was carried out on a tissue microarray of 92 cases of invasive urothelial carcinoma of the bladder (≥ pT2) using antibodies against phospho-S6 and phospho-4E BP1, both markers for an activated mTOR pathway. Staining was graded as 0 to 3+ (0=0-5%; 1+=6-25%; 2+=26-50%; and 3+=>50% tumor cells positive) for phsopho-S6 (cytoplasmic) and phospho-4E BP1 (cytoplasmic and/or nuclear). Presence of at least two evaluable cores from each tumor was required for inclusion in the final evaluation. The results of immunoreactivity in tumor cells demonstrated that mTOR pathway markers are overexpressed in invasive urothelial carcinoma of the bladder with correlation of expression seen within molecules of the mTOR pathway using Spearman's correlation coefficient (rho=0.411) (see table below). This suggests that m-TOR targeted therapies may have activity in patients with urothelial carcinoma.

Table 2. Tumor cell immunoreactivity

Antibody (# cases)	**Grade 0 (%)**	**Grade 1+ (%)**	**Grade 2+ (%)**	**Grade 3+ (%)**
p-S6 (85)	45 (53)	11 (13)	9 (11)	20 (23)
p-4E BP1 (84)	25 (30)	10 (12)	17 (20)	32 (38)

3.4 Everolimus

Everolimus is a novel oral derivative of rapamycin.

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the

European Union. Everolimus has been in development for patients with various malignancies since 2002.

Everolimus is being investigated as an anticancer agent based on its potential to act:

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation.
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

3.4.1 mTOR pathway and mechanism of action

At the cellular and molecular level, Everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), a key and a highly conservative serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of Everolimus (reviewed in Boulay and Lane, 2007).

mTOR is downstream of PI3K/AKT pathway, a pathway known to be dysregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness, resistance to treatment and progression.

The main known functions of mTOR include the following (Bjornsti and Houghton 2004; Boulay and Lane, 2007):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.
- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates translation of important massages, including those encoding the HIF-1 proteins, c-myc, ornithine decarboxylase, and cyclin D1, as well as ribosomal proteins themselves.
- The activation of mTOR pathway leads to the increased production of pro-angiogenic factors (i.e., VEGF) in tumors and to tumor, endothelial and smooth muscle cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive) (Wullschleger, Loewith and Hall 2006).

mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2) (Bjornsti and Houghton 2004). Activated AKT phosphorylates TSC2, which leads to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1 (Manning and Cantley 2007; Wang at al 2007).

mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signaling (Manning and Cantley 2007). It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT that is not upstream of mTORC1. PHLPP phosphatase plays the role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton (Wullschleger, Loewith and Hall 2006).

mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as Everolimus. Once these agents bind to the 12 kDa cytosolic FK506-binding protein immunophilin FKBP12, the resulting rapamycin-FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity (Witzig, et al 2005). Since many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis (Bjornsti and Houghton 2004).

3.4.2 Preclinical studies

Pre-clinical investigations have demonstrated that Everolimus is a potent inhibitor of the proliferation of a range of human tumor cell lines *in-vitro* with IC50s ranging from sub/low nM to µM concentrations. These concentrations can be reached in patients at the doses used in clinical trials.

Everolimus has proven active in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. Everolimus was also shown to have activity in acute myeloid leukemia cells (Zeng, et al 2007), adult T-cell leukemia cells (Ikezoe, et al 2007), diffuse large B cell lymphoma cells (DLBCL; Wanner, et al 2006), pancreatic tumor cells (Tuncyurek, et al 2007), ovarian cancer cells (Treeck, et al 2006, Mabuchi, et al 2007), hepatocellular carcinoma cells (Sieghart, et al 2007), and human pancreatic neuroendocrine cells, where induction of apoptosis was reported (Zitzmann, et al 2007).

As a single agent, Everolimus inhibited proliferation in three mantle cell lymphoma cell lines (Jeko1, SP49 and NCEB1) approximately 40–65% compared to control cells. This was associated with G1 cell-cycle arrest and reduced phosphorylation of the mTOR downstream target, 4E-BP1 (Haritunians, et al 2007).

In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma), Everolimus inhibited colony formation in a concentration-dependent manner. In addition, normal hematopoetic stem cells were insensitive to Everolimus, with an IC50 about 15 times higher than the tumor lines.

Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF-induced proliferation. The inhibition of endothelial proliferation and antiangiogenic activity of Everolimus has been confirmed *in vivo*, as Everolimus selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls at well-tolerated doses. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

Everolimus also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of Everolimus monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease.

Everolimus, administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- s.c. mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170-overexpressing multi-drug resistant tumor line.
- a series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3 lines), lung (22 lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines).
- two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma).

Taken together, these data indicate the broad antiproliferative potential of Everolimus.

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

In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4E-BP1, and occasionally with an increase in phosphorylation AKT (pAKT).

3.3.3 Pre-Clinical Safety

In safety pharmacology studies, Everolimus was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. Everolimus had no influence on QT interval prolongation. Furthermore, Everolimus showed no antigenic potential. Although Everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of Everolimus to affect vital functions in patients is considered low.

Everolimus is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with Everolimus in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and were at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species-specific disorder.

More pre-clinical information is provided in the Investigator's Brochure.

3.3.4 Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median t_{max} of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The $AUC_{0-\tau}$ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. C_{max} is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in C_{max} is less than dose-proportional. The coefficient of variation between patients is approximately 50%.

Trough levels (24 hour post-dose) correlate well with $AUC_{0-\tau}$ at steady-state during daily administration.

In whole blood, at a daily dose of 10 mg, about 20% of Everolimus is confined in plasma with 26% being unbound. The remaining 80% is sequestered in blood cells.

Everolimus is extensively metabolized in the liver and eliminated in the bile. Major metabolites are inactive. Elimination half-life is approximately 30 hours. The clearance of Everolimus is approximately halved in patients with mild-moderate hepatic impairment (Child-Pugh Class A or B), while renal impairment has little or no impact on its the pharmacokinetics.

Age, weight and gender in the adult population do not affect the pharmacokinetics of Everolimus to a clinically relevant extent. The clearance of Everolimus is reduced in children.

Pharmacokinetic characteristics are not notably different between Caucasian and Japanese subjects, whereas population pharmacokinetic studies have shown an average 20% higher clearance in Black patients.

A high-fat meal altered the absorption of Everolimus with a 1.3 hour delay in t_{max}, a 60% reduction in C_{max} and a 16% reduction in AUC.

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of the multi-drug efflux pump P-glycoprotein (P-gP, MDR1, ABCB1). Hence, its metabolism is sensitive to drugs which modify these enzymes (substrates, inducers, or inhibitors of these enzymes). Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 or P-glycoprotein substrates.

Table 6 (Section 9.5) lists examples of clinically relevant CYP3A inhibitors and inducers.

Please refer to Section 9.5 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

More information on Everolimus pharmacokinetics is provided in the [Investigator's Brochure].

3.3.5 Everolimus Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high degree of sustained target inhibition ([Study C2101] / [Study 2102], Lane, et al 2003). Furthermore, molecular pharmacodynamic (MPD) studies using immunocytochemistry (IHC) in biopsied tumor tissue assessed the degree of inhibition and its duration for pS6, p4E-BP1 and pAKT expression with the daily and weekly dosing. There was high inhibition of the downstream markers S6K1 and 4E-BP1 at 5mg/day, which was complete at 10 mg/day, while preliminary results suggest an increase in pAKT expression with maximal effect at 10 mg daily ([Study C2107], Tabernero, et al 2005).

More information is provided in the Investigator's Brochure.

3.3.6 Clinical experience with Everolimus

Everolimus has been investigated as a component of multi-drug immunosuppression in solid organ transplantation since 1996 and was approved for the indication of prophylaxis of organ rejection in adult patients receiving an allogeneic renal or cardiac transplant on 8 Jul 2003 by the European Union under the trade name of Certican®. The most frequent adverse drug reactions in this context are highly specific to the transplant context. However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels.

Everolimus has been in development for patients with cancer since 2002. Approximately 2586 patients with various malignancies have been treated in either Novartis-sponsored or non-Novartis-sponsored clinical studies as of 31 Aug 2007. Overall, Novartis sponsored a total of 22 studies of Everolimus administered either as a single agent (n=848) or in combination with other anti-tumor agents (n=663). Ongoing or completed Investigator-sponsored studies also enrolled over 1000 patients globally.

Eight single-agent Novartis sponsored trials have or are being conducted in various advanced malignancies. Five Phase I studies evaluated several escalating doses with either weekly or daily administration (Studies C2101/02, C2106, C2107, C1101) of Everolimus with the objective to identify an optimal regimen and dosage based on safety, pharmacokinetics, and knowledge of the drug's molecular effects on various tumors. The 10 mg/day and 50-70 mg/week dosages were proposed for further studies when using Everolimus as a single agent and as a target maximum dose in combination studies. In addition, the Phase I studies conducted in prostate cancer (Study C2106) and in Japanese patients with advanced cancers (Study C1101) evaluated the safety and the molecular changes in tumors associated with the administration of Everolimus.

Two Phase II monotherapy studies were designed to evaluate the safety and efficacy of a single dose of 10 mg administered daily, including Study C2235 in advanced NSCLC (n=81) and Study C2239 in advanced pancreatic neuroendrine tumors (n=160).

A Phase III study (Study C2240) is ongoing and designed to demonstrate the safety and efficacy of Everolimus at an oral dose of 10 mg versus matching placebo in patients with metastatic carcinoma of the kidney, whose disease has progressed despite prior VEGF-R tyrosine kinase inhibitor therapy. Over 400 patients have been enrolled in this prospective, randomized, multicenter study, which remains blinded as of the cut-off date.

Overall, the most frequent mild-moderate Grade 1 and 2 adverse effects have been rash, stomatitis, fatigue, neutropenia and, to a lesser extent, gastrointestinal disorders (nausea, anorexia, diarrhea, vomiting) and headache. The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia. Reduced blood counts, hyperlipidemia (mainly hypercholesterolemia), and hyperglycemia are relatively frequent laboratory findings. Infections have not been notably frequent or severe. Severe non-infectious low-Grade (Grade 1 and 2) pneumonitis has led to development of treatment guidelines for the disorder (Table 3-2). Preliminary indications of anti-tumor activity are encouraging.

Refer to Section 9 for more information on known undesirable effects of Everolimus.

Further detailed information regarding Everolimus clinical development, safety and efficacy is provided in the [Investigator's Brochure].

3.3.7 Rationale for the Study Population

The first-line treatment of patients with metastatic urothelial carcinoma varies and may involve a cisplatin- or carboplatin-based doublet, triplet, the four drug MVAC regimen, or a sequential doublet regimen. Furthermore, many patients with metastatic disease have previously received cytotoxic chemotherapy in the perioperative setting. Given this heterogeneity in prior exposure to chemotherapy, the definition of "second-line" or "third-line" chemotherapy has not been well characterized. As a result, we have designed the eligibility for this protocol based on the number of prior chemotherapeutic agents patients have received rather than the number of "lines" of therapy that have been administered. Second-line chemotherapy trials have typically included patients who have received either 1 or ≥ 1 prior regimen(s). Clinical trials at MSKCC have included a maximum of 4 prior drugs because patients are treated with multiple agents in the community before referral. There are no available data demonstrating that the response proportion in the relapsed setting is linked to the number of prior regimens; this concept has been

reinforced identifying Sunitinib as active in a MSKCC phase 2 trial of patients with metastatic urothelial cancer who have received a maximum of 4 prior drugs (J Clin Oncol 2008 Vol. 26, No 15S, p. 270s Abstract #5082). This prior treatment inclusion criteria will serve to enhance accrual and likely ultimately provide a more homogenous patient population (e.g., most patients will have been exposed to a platinum, gemcitabine, and a taxane at some point in their treatment history). Further, we do not anticipate the response to this targeted agent to be closely linked to the number of prior cytotoxic agents administered. If Everolimus demonstrates activity in this second-line trial, future trials will include an evaluation of the combination of Everolimus with chemotherapy in the first- and second-line settings.

3.3.8 Rationale for a PFS Endpoint

Pertinent to the issue of discovering new drugs active in urothelial cancers is that identifying clinical benefit should not be limited to response. Some of the newer "targeted therapy" agents approved by the FDA have been approved on the basis of improved progression-free survival (PFS) and not response rate (e.g., sorafenib in renal cell carcinoma with a response rate of approximately 10% but a major impact in PFS and, eventually, an improvement in survival). This being said, the median progression-free survival for bladder cancer patients treated with chemotherapy is modest at only 2-3 months and response rates are in the 10-20% range. In a second-line trial of weekly paclitaxel in 31 patients with progressive urothelial cancer, the median time to progression was 2.2 months[4]. In an ECOG trial evaluating the epothilone analog BMS-247550 in patients with relapsed urothelial cancer, the median progression-free survival was 2.7 months (95% CI, 1.8, 4.1)[5]. In a recently reported phase 3 randomized second-line trial of vinflunine versus best supportive care, the PFS for patients treated with vinflunine was 3.0 months (95% CI, 2.1, 4.0) (J Clin Oncol 2008 Vol. 26, No 15S, p. 257s Abstract #5028). Novel therapies are desperately needed for these patients and identifying activity in the refractory setting by using PFS is considered an acceptable approach with these new targeted agents.

A recently reported randomized, double-blind, multicenter trial of Everolimus versus placebo has demonstrated a statistically and clinically significant improvement in progression-free survival (HR=0.30, p <0.0001), with a favorable safety profile in patients with metastatic renal cell carcinoma after progression on VEGFr-TKI therapy ((J Clin Oncol 2008 Vol. 26, No 15S, p. 256s Abstract #LBA5026). Based on a sample size of 362 patients, this trial had a 90% power to detect a 33% risk reduction with a median exponential PFS improvement from 3.0 to 4.5 months. The PFS for Everolimus-treated patients was 4.0 months (3.7-5.5) versus 1.9 months (1.8-1.9) for those treated with placebo. Pertinent to this study, only 3% of patients had a partial response by RECIST and the majority of patients had stable disease. Also pertinent to this proposed trial in bladder cancer is the fact that the kidney cancer trial was also not a pure “second-line” trial; approximately 50% of patients had received more than one prior TKI. Everolimus was well–tolerated, with the most common adverse events including stomatitis, anemia and asthenia. This trial establishes precedent for the use of PFS as an endpoint for RAD001 trials in other diseases in the “second-line” setting.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is an open-label Phase II study of Everolimus in patients with progressive advanced/metastatic urothelial carcinoma that have progressed despite treatment with prior cytotoxic chemotherapy.

The primary endpoints of this study will be:

- To measure the two-month PFS rate of Everolimus (RAD001) as determined by RECIST
- To determine the safety and toxicity of Everolimus (RAD001) in this patient population

The secondary endpoints of this study will be:

- To determine the response rate of Everolimus in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy.
- To assess markers for activated mTOR pathway (including phospho-S6 and phsopho-4E BP1) in all pre-treatment tissue specimens and correlate with response to treatment and PFS.

4.3 Intervention

Everolimus will be administered at a dose of 10 mg orally once daily continuously. Intra-patient dose reduction may be required depending on the type and severity of the individual toxicity encountered. Re-staging imaging studies will be performed after every two cycles of treatment (one cycle = 4 weeks) during the first five years of treatment, and after every 3-6 cycles of treatment thereafter. Patients may continue on study as long as they are tolerating therapy and are free of disease progression.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Investigational Drug Description

Everolimus (RAD001) is a novel oral derivative of rapamycin. Everolimus will be administered orally as a once-daily dose of 10 mg (two 5 mg tablets) continuously from study day 1 until progression of disease or unacceptable toxicity. Patients will be instructed to take Everolimus in the morning, at the same time each day.

Everolimus should be taken by the patient in a fasting state or with no more than a light fat-free meal. Dietary habits around the time of Everolimus intake should be as consistent as possible throughout the study.

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

5.3 Drug Dispensing/Administration

Administration will be performed on an outpatient basis. Everolimus will be dispensed as tablets at the beginning of each treatment cycle (or, for patients who have completed five years of treatment, at the beginning of every other treatment cycle). In case of dose modification, patients will be asked to return all of their previously dispensed medication to the clinic and they will be dispensed with new strength capsules.

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

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

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

5.4 Storage and Stability

Current stability data permit a shelf life of either 36 months (for 5mg tablet variants based on solid dispersion dried by evaporation/drying oven) or 24 months (for 2.5mg, 5 mg and 10 mg tablet variants based on solid dispersion dried by paddle dryer), assuming correct storage below 30^{o}C in the original double-sided aluminium blister packaging and protected from light and moisture.

5.5 Source of Drug

Novartis, Inc. will supply Everolimus free of charge.

5.6 Drug Accountability

All study drug supplies must be kept in a locked room with limited access. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Novartis.

The pharmacist will maintain a complete drug accountability record for each capsule strength with lot numbers of each drug received, including the number of bottles dispensed to each patient, the dates drug was dispensed, and the daily dose of Everolimus the patient received. The prescribed dose should also be recorded in the patient's medical records.

At the conclusion of the study, all unused Everolimus tablets will be destroyed on-site as described in a standard operating procedure for the destruction of chemotherapeutic waste.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

6.2 Subject Inclusion Criteria

- Patients must have a diagnosis of urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis, with histological confirmation at MSKCC.
- Patients must have progressive metastatic disease. Progressive disease will be defined as new or progressive lesions on cross-sectional imaging.
- Patients must have at least one measurable site of disease (according to RECIST criteria) that has not been previously irradiated. If the patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation.
- Patients must have been previously treated, as defined by the following:
    - Treatment with <u>at least</u> one prior cytotoxic agent but <u>not</u> more than four prior cytotoxic agents. Up to four prior chemotherapy agents are allowed, since conventional chemotherapy ranges from just one drug (e.g., gemcitabine) to regimens that contain four agents (e.g., M-VAC is a four-drug regimen containing methotrexate, vinblastine, doxorubicin, and cisplatin).
    - The prior therapy must have included at least one of the following: cisplatin, carboplatin, paclitaxel, docetaxel, or gemcitabine.
    - The prior cytotoxic agents may have been administered in the perioperative or metastatic setting and may have been administered sequentially (e.g., first-line treatment followed by second-line treatment at time of progression) or as part of a single regimen.
- Pre-treatment tumor tissue available for analysis of m-TOR pathway markers
- Age $\geq$ 18 years
- Karonfsky Performance Status $\geq$ 60%
- Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L, Hb >9 g/dL
- Adequate liver function as shown by:
    - serum bilirubin $\leq$ 1.5 x ULN

  - INR < 1.3 (or < 3 on anticoagulants)
  - ALT and AST ≤ 2.5x ULN (≤ 5x ULN in patients with liver metastases)
- Adequate renal function: serum creatinine ≤ 1.5 x ULN
- Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: If a patient's lipid values exceed either one of these criteria upon screening, the patient can only become eligible after successful initiation of appropriate lipid-lowering medication. After lipid-lowering therapy, patients must meet the same criteria – i.e. a fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN – to be eligible for study treatment.
- Signed informed consent
- Testing for hepatitis B viral load and serological markers (HBV-DNA, HBsAg, HBsAb, and HBcAb) for the following patients:
  - All patients who currently live in (or have lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, or Greece
  - Patients with any of the following risk factors:
    - Known or suspected past hepatitis B infection
    - Blood transfusion(s) prior to 1990
    - Current or prior IV drug users
    - Current or prior dialysis
    - Household contact with hepatitis B infected person(s)
    - Current or prior high-risk sexual activity
    - Body piercing or tattoos
    - Mother known to have hepatitis B
    - History suggestive of hepatitis B infection, e.g dark urine, jaundice, or right upper quadrant pain
  - Additional patients at the discretion of the investigator
- Testing for hepatitis C infection (using quantitative RNA-PCR) for patients with any of the following risk factors:
  - Known or suspected past hepatitis C infection (including patients with past interferon "curative" treatment)
  - Blood transfusion(s) prior to 1990
  - Current or prior IV drug users
  - Household contact of hepatitis C infected person(s)
  - Current or prior high-risk sexual activity
  - Body piercing or tattoos
  - Additional patients at the discretion of the investigator

6.2 Subject Exclusion Criteria

- Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks of the start of study drug (including chemotherapy, radiation therapy, antibody based therapy, etc.)
- Patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia), or patients who may require major surgery during the course of the study
- Prior treatment with any investigational drug within the preceding 4 weeks
- Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent, except corticosteroids with a daily dosage equivalent to prednisone ≤ 20 mg. Patients receiving these corticosteroids must have been on a stable dosage regimen for a minimum of 4 weeks prior to the first treatment with Everolimus. Topical or inhaled corticosteroids are allowed.
- Patients should not receive immunization with attenuated live vaccines within one week of study entry or during study period
- Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases
- Evidence of another active cancer, except for non-melanoma skin carcinoma, in-situ carcinoma of the cervix curatively treated, and adenocarcinoma of the prostate that has been surgically treated with a post-treatment PSA that is non-detectable.
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Symptomatic congestive heart failure of New York Heart Association Class III or IV
    - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months of start of study drug, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
- Severely impaired lung function as evidenced by:
    - TLC <50% predicted OR
    - FVC <50% predicted OR
    - DLCO <40% predicted
- Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
- Active (acute or chronic) or uncontrolled severe infections
- Liver disease such as cirrhosis, chronic active hepatitis, or chronic persistent hepatitis
- A known history of HIV seropositivity
- 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)
- Patients with an active, bleeding diathesis

- Female patients who are pregnant or breast-feeding. Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to administration of Everolimus.
- Adults of reproductive potential who are not using effective birth control methods. Men and women of childbearing potential must be willing to use effective barrier method contraception during the trial and for at least three months thereafter. Patients are encouraged to continue barrier method contraception for two years or longer after treatment. Hormonal contraceptives are not acceptable as a sole method of contraception.
- Patients who have received prior treatment with an mTOR inhibitor (sirolimus, temsirolimus, everolimus).
- Patients with a known hypersensitivity to Everolimus (RAD001) or other rapamycins (sirolimus, temsirolimus) or to its excipients
- History of noncompliance to medical regimens
- Patients unwilling to or unable to comply with the protocol

7.0 RECRUITMENT PLAN

Patients will be recruited from the outpatient clinics of the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center (MSKCC). Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The patient's initial conversation with the investigator/research staff and portions of the patient's MSKCC medical records will be used to confirm that the patient is eligible for study participation.

8.1 PRETREATMENT EVALUATION

The following will be completed within 14 days prior to initiation of treatment (unless otherwise indicated):

- Complete history and physical examination with measurements of all palpable lesions and review of all concomitant medications
- Height, weight, body surface area
- Karnofsky Performance Status
- Complete blood count (CBC) with differential and platelets
- Comprehensive panel, i.e. serum electrolytes including sodium, potassium, chloride,

bicarbonate, phosphorus, calcium, glucose, blood urea nitrogen, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, total protein, albumin, and uric acid

- PT/PTT
- Fasting Lipids include triglycerides, total cholesterol, HDL and LDL
- Pregnancy test in women of childbearing age
- EKG (within 30 days)
- Baseline abdominal and pelvic CT scans or MRI for abdominal or pelvic indicator lesions (within 30 days)
- In patients with osseous lesions, bone X-rays and/or bone scans should be obtained (within 30 days)
- Chest X-ray (a CT of chest may be performed instead if clinically relevant) (within 30 days)
- Pulmonary function tests (within thirty days)
- Pre-treatment tumor tissue specimens for all patients will be analyzed using immunohistochemistry for markers including those of an activated mTOR pathway including phsopho-S6 and phospho-4E BP1. Staining will be graded as 0 to 3+ (0 = 0-5%; 1+ = 6-25%; and 3+ = >50% tumor cells positive) by the Core Lab of the MSKCC Department of Pathology. The study will not require research biopsies.
- Hepatitis B testing (HBV-DNA, HBsAg, HBsAb, and HBcAb) for all patients who meet the hepatitis B risk criteria outlined in Section 6.1.

Hepatitis C testing (quantitative RNA-PCR) for all patients who meet the hepatitis C risk criteria outlined in Section 6.1.

9.1 TREATMENT/INTERVENTION PLAN

9.2 Schedule and Dose Administration

The study drug Everolimus will be self-administered on an outpatient basis. The investigator will instruct the patient to take the study drug exactly as specified in the protocol section 5.1. Everolimus will be administered orally as a once-daily dose of 10 mg (Two 5 mg tablets) continuously from study day 1 until progression of disease or unacceptable toxicity.

The start of the next cycle may be delayed if additional time is required for the patient to recover from Everolimus-associated toxicity experienced during the previous cycle. However, imaging will occur at regular intervals. The study investigator may implement dose suspension or reduction in order to ensure patient safety (see section 9.2).

9.3 Dose Modifications

Patients will be monitored closely for toxicity, and the Everolimus dose may be adjusted according to individual patient tolerance. For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug.

If administration of Everolimus must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Table 4. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, http://ctep.cancer.gov/forms/CTCAEv3.pdf).

Table 3. Everolimus dose level modification guidelines

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

Table 4. Criteria for dose-modification in case of suspected Everolimus toxicity and re-initiation of Everolimus treatment

Toxicity	Actions
Non-hematological toxicity	
Grade 2 (except pneumonitis – refer to Table 5	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, interrupt Everolimus until recovery to grade ≤1, then reintroduce Everolimus at the lower dose level.
Grade 3 (except hyperlipidemia*)(except pneumonitis – refer to Table 5	Interrupt Everolimus until recovery to grade ≤1, then reintroduce Everolimus at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4 (including hyperlipidemia)	Discontinue Everolimus.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt Everolimus until recovery to grade ≤1 (>75 x10^9/L), then reintroduce Everolimus at initial dose. If thrombocytopenia again returns to grade 2, interrupt Everolimus until recovery to grade ≤1. Then reintroduce Everolimus at the lower dose level.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt Everolimus until recovery to grade ≤1 (platelets ≥ 75 x10^9/L). Then resume Everolimus at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue Everolimus.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue Everolimus.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 x10^9/L)	Interrupt Everolimus until recovery to grade ≤1 (neutrophils ≥ 1.5 x 10^9/L), then resume Everolimus at the initial dose. If ANC again returns to Grade 3, hold Everolimus until the ANC ≥ 1.5 x 10^9/L, then resume Everolimus dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt Everolimus until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 10^9/L). Then resume Everolimus at the 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 ≤ 1. Hold further Everolimus until the ANC ≥ 1,500/mm^3 and fever has resolved. Then resume Everolimus at the lower dose level. If febrile neutropenia recurs, discontinue Everolimus.
Grade 4 febrile neutropenia (life-threatening)	Discontinue Everolimus.
Any hematological or non-hematological toxicity requiring interruption for ≥ 3 weeks	Discontinue Everolimus.

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 9.3.2).

9.3 Monitoring of Everolimus suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or an abnormal laboratory value suspected to be related to Everolimus must be followed at least weekly until the adverse event or abnormal laboratory value resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

9.3.1 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care.

When described, the disorder has been identified as inflammation or ulcers in the mouth. If exam reveals mouth ulcers, rather than a more general inflammation of the mouth, please classify the adverse event as 'mouth ulcers.' If inflammation is limited to the mouth without ulcers, please use the term 'stomatitis' rather than the less specific term 'mucositis.'

If the disorder appears elsewhere other than the mouth, please describe the location as well as any specific procedures carried out for exploration (e.g. endoscopy).

Please use the Grading according to the NIH-NCI Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0; http://ctep.cancer.gov/forms/CTCAEv3.pdf).

Grade 1: minimal symptoms; normal diet

Grade 2: symptomatic but can eat and swallow modified diet

Grade 3: symptomatic and unable to adequately aliment or hydrate orally

Grade 4: symptoms associated with life-threatening consequences

Recommendations:

1. For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouthwash or salt water (0.9%) mouthwash several times a day until resolution.
2. For more severe toxicity (Grade 2 or 3), 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% (e.g. 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.

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 (which leads 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.

9.3.2 Management of 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 higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 or higher hypertriglyceridemia (>2.5 x upper normal limit) should be treated with a statin 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. Patients who develop grade 4 hyperglycemia or grade 4 hyperlipidemia will be withdrawn from study.

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 kinase (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. In many cases in [Study Everolimus C2222] the affected patients had an abnormal fasting glucose at baseline. Based on this finding, optimal glucose control (indicated by fasting triglycerides ≤ 2.5 x ULN) must be achieved before starting a patient on Everolimus. Study patients should have their glucose levels monitored during Everolimus therapy.

9.3.3 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving Everolimus therapy. Non-infectious pneumonitis has been associated with Everolimus and other mTOR inhibitors (Atkins 2004). All patients are required to undergo baseline/pretreatment pulmonary function tests and will be excluded from study treatment if TLC <50% predicted, FVC <50% predicted, or DLCO <40% predicted. In order to monitor for asymptomatic (grade 1) non-infectious pneumonitis during study treatment, a chest CT scan or chest x-ray is required in addition to the monthly radiological tumor examinations. Additional chest CT scans may be performed when clinically necessary. If non-infectious pneumonitis develops, a consultation with a pulmonologist should be considered. If the patient develops grade 3 pneumonitis, treatment with Everolimus should be interrupted and the patient should be treated as medically indicated (short course corticosteroids, oxygen, etc).

Management of non-infectious pneumonitis suspected to be associated with Everolimus and dose modification instructions are provided in Table 5.

The attribution of changes on interval chest imaging will be recorded as related, possibly related, or unrelated to study drug.

Table 5 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_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required.	Administer 100% of Everolimus dose.
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy. *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Reduce Everolimus dose until recovery to ≤ Grade 1. Everolimus may also be interrupted if symptoms are troublesome. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 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 ≤ Grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 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.

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

9.3.4 Management of hepatitis B

Table 6 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 6 Action to be taken for positive baseline hepatitis B results

Test	Result	Result	Result	Result	
HBV-DNA	+	+ or -	-	-	
HBsAg	+ or -	+	-	-	
HBs Ab	+ or -	+ or -	+ and no prior HBV vaccination	+ or -	- or + with prior HBV 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 weeks				No specific action

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

For patients who have already been randomized and received study drug prior to the approval of the amendment, the same process should be followed at the patient's next visit. The first HBV-DNA result would be regarded as baseline.

For hepatitis B reactivation, definition and management guidelines, see Table 3-2 Guidelines for management of hepatitis B.

Table 7 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBsAg --- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA] AND ALT elevation x 5 ULN	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: • ≤ grade 1 ALT (or baseline ALT, if > grade 1) and • ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days, study drug should be re-started at one dose level 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 > 28 days, patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
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] --- reactivation is defined as: New appearance of measurable HBV-DNA	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 level 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. 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 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation). 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 ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

9.3.5 Hepatitis C management

The following two categories of patients should be monitored every 4 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 8.

Table 8 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 v 3.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 3.0 Metabolic Laboratory/Other: Viral Re-activation).

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If, for any patient, either study treatment or observations are discontinued, the reason will be recorded.

9.4 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

9.5 Concomitant Medications

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

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

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

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Growth factors (e.g.G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to

be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events if this is thought to be appropriate.

- Concurrent administration of Everolimus and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of Everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Competitive inhibition could occur when Everolimus is combined with drugs which are also CYP3A4 substrates. Caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of Everolimus).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with systemic steroids or immunosuppressive agents except corticosteroids with a daily dosage equivalent to prednisone $\leq$ 20 mg should be administered. Patients receiving corticosteroids must have been on a stable dosage regimen for a minimum of 4 weeks prior to the first treatment with Everolimus. Topical or inhaled corticosteroids are allowed.
- Everolimus may affect the response to vaccinations, making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with Everolimus.

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

Examples are provided in Table 6. A comprehensive list of cytochrome P450 isoenzymes and CYP3A4 inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/flockhart. This website is continually revised and should be checked frequently for updates.

Table 6. Examples of clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A.

Substrates (competitive inhibition)	
Antibiotics[1]: clarithromycin* erythromycin telithromycin* Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir* ritonavir* saquinavir* Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine27	Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors[2]: atorvastatin cerivastatin lovastatin simvastatin Miscellaneous: aprepitant buspirone haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine
Inducers	
Carbamazepine Phenobarbital Phenytoin* Rifabutin*	Rifampin* St John's wort Troglitazone
Inhibitors	
Amiodarone Atanzavir Cimetidine Ciprofloxacin Clarithromycin Conivaptan* Darunavir Delaviridine Diltiazem Erythromycin Fluconazole Fluvoxamine* Grapefruit juice Sevilla orange Posaconazole*	Indinavir Itraconazole* Ketoconazole* Lopinavir* Voriconazole* Posaconazole* Mibefradil* Nefazodone* Nelfinavir* Troleandomycin* Verapamil Voriconazole* Imatinib Tofisopam

Based on: Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn Schmiedebergs Arch Pharmacol. 2004 Jan;369(1):89-104. [http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006], Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Dec. 2, 2009, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug

Interaction Table. "

* asterisk denotes strong inhibition/induction

Please note:

- strong inhibitor implies that it can cause ≥5-fold increase in AUC or ≥80% decrease in clearance of sensitive CYP substrates
- moderate inhibitor implies that it can cause 2- to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates.

  (Distinction is not always categorical as interaction can vary according to conditions).

1. Macrolide antibiotics: Azithromycin is not a CYP3A substrate. Therefore, it may be employed where antibiotherapy with a macrolide is desirable in a patient being treated with Everolimus.
2. Statins: Atorvastatin and pravastatin may be associated with Everolimus, since a PK interaction study has shown that there is no relevant PK interaction.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 7. Schedule of Events

	Screening		Cycle 1			Additional Cycles (Years 1-4)		Additional Cycles (Years 5+)		Post Treatment/ Withdrawal[7]	Survival Follow-up
Procedure	≤ 30 Days Prior to Dosing	≤ 14 Days Prior to Dosing	Day 1 (± 3)	Day 14 (± 3)	Day 28 (± 3)	Day 1 (± 3)	Day 28 (± 3)	Day 1 (± 3)	Day 56 (± 3)		
Informed Consent		X									
Medical History		X									
Physical Examination, KPS		X	(X)[6]	X		X		X[15]		X	
Lab Studies											
Pregnancy Test[9]		X									
Hematology[1]		X	(X)[6]	X		X		X[15]		X	
Biochemistry[2]		X	(X)[6]	X		X		X[15]		X	
PT/PTT		X									
Fasting Lipids[2]		X	(X)[6]			X		X[15]		X	
HBV-DNA, HBsAg, HBs Ab, HBs Ab, HCV-RNA-PCR[12]	X										
HBV DNA, HCV RNA-PCR[13]			X			X		X		X	
Other Assessments											
12-lead EKG	X										
Pulmonary Function Tests	X										
Disease Assessment/Tumor measurements[3]	X						X[3]		X[14]	X	
Adverse Events[4]			X	X		X		X[15]		X	
Concomitant Medications		X	X	X		X		X[15]		X	
Treatment compliance[11]					X		X		X		
Everolimus[8]			X →	→	→	→	→	→	→		
Survival Status[5]											X
Tumor Tissue Evaluation[10]	X										

(X) – if applicable X → - start and continue treatment → - continue treatment

Footnotes for Schedule of Events
1.Complete blood count (CBC) with differential and platelets
2. Comprehensive panel (i.e. serum electrolytes including sodium, potassium, chloride, bicarbonate, phosphorus, calcium, glucose, blood urea nitrogen, creatinine, SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, total protein, albumin, uric acid). Fasting Lipids include triglycerides, total cholesterol, HDL and LDL.
3. Disease Assessment/Tumor Measurements: Re-staging imaging studies will be performed after every two cycles of treatment (1 cycle = 4 weeks) during the first five years of treatment and after study completion or withdrawal. Imaging studies should be performed during weeks 7 or 8. The same imaging studies performed at baseline (e.g., CT or MRI) should be performed throughout the study, when possible. Baseline chest CT or chest x-ray must be performed. If chest CT or chest x-ray is not part of the disease assessment, it must be repeated every 2 months. Bone x-ray(s)/scan to be performed if bone metastases are present.
4. Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.
5. Post-study survival status: Follow-up survival information will be collected for all patients by clinic visit or telephone contact approximately every 6 months for up to 2 years from the date of first dose of Everolimus. Patients will be followed until disease progression and/or death.
6. Physical Examination/Hematology/Biochemistry/Fasting Lipids: Physical Examination/ Hematology/ Biochemistry/Fasting Lipids on Cycle 1 Day 1 is not required if performed within 7 days of Day 1 unless clinically indicated.
7. Post Treatment/Withdrawal: This visit will take place 1 month after the last dose of study drug. Patients with ongoing study drug-related toxicities should be followed as dictated in footnote 4. These patients should be followed at the interval deemed appropriate by their study physician.
8. Everolimus: Everolimus will be orally self-administered, once daily in the morning. Patients will receive a prescription for a 4-week supply of drug at the beginning of each cycle during their first five years of treatment. After five years of treatment, patients will receive a prescription for an 8-week supply of drug at the beginning of every other cycle. The Everolimus drug bottles (including any unused capsules) will be returned to the clinic for drug accountability at each study visit.
9. Serum or urine test must be performed for all women of childbearing potential.
10. Pre-treatment tumor tissue specimens for all patients will be analyzed using immunohistochemistry for markers including those of an activated mTOR pathway including phsopho-S6 and phospho-4E BP1. Note that the study will not require research biopsies.
11. Treatment Compliance: At the start of each cycle, patients will be given a Pill Diary and asked to record the time, date, concomitant drugs, and side-effects of each dose of Everolimus taken.
12. All patients should be screened for hepatitis risk factors and any past illnesses of hepatitis B and hepatitis C. It is highly recommended that patients with positive HBV-DNA or HBsAg are treated prophylactically with an antiviral for 1-2 weeks prior to receiving study drug. The antiviral treatment should continue throughout the entire study period and for at least 4 weeks after the last dose of study drug. Patients with viral hepatitis C risk factors should be screened for HCV RNA-PCR.
13. Patients on antiviral prophylaxis treatment or positive HBV antibodies should be tested for HBV-DNA according to study visit schedule. Patients with positive HCV-RNA PCR or a history of past infection, even if treated and considered 'cured' – should be followed by HCV-RNA PCR according to visit schedule.

14. Patients who complete five years of study treatment will undergo imaging studies as directed in Footnote 3 after every 3-6 cycles of treatment as determined by their treating physician.
15. Patients who complete five years of study treatment will return to clinic for physical exam, KPS, laboratory assessments, adverse events assessment, and concomitant medications assessment every two cycles (56 +/- 3 days).

11.0 TOXICITIES/SIDE EFFECTS

Adverse events most frequently observed with Everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, and diarrhea. Infections have not been notably frequent or severe. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts and hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia.

The principal DLT in Phase 1 trials has been Grade 3 stomatitis. For guidance on management of stomatitis refer to Section 9.3.1

Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting; this aspect must be verified when interpreting results. For guidance on management of hyperlipidemia refer to Section 9.3.2.

Hyperglycemia was reported as a serious adverse reaction. Again, the fasting state of patients should be verified when interpreting results. For guidance on management of hyperglycemia refer to Section 9.3.2.

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 radiologically evident, non-infectious, non-malignant infiltration in the lungs. More precise diagnosis should come after histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic. Advice on the management of pneumonitis has been provided in Table 5.

In oncology studies with Everolimus, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions. Additionally, it has been reported in the following associated preferred terms: acute respiratory distress syndrome (n=2), alveolitis (n=1), allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alvealoar haemorrhage, pulmonary toxicity, and pulmonary fibrosis (n=1 each). One fatal case of drug-related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting Everolimus. Cytology for both the pleural and pericardial fluids were positive for malignancy. The death was considered possibly related to the underlying late-stage tumor and study drug. Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung.

Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with Everolimus: mycobactrium, aspergillus, fatal candidal sepsis, and fatal pneumocystis carnii, in particular. Because Everolimus, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts,

treatment with Everolimus must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections.

A reduction in blood cell counts is frequent when Everolimus therapy is initiated. Infrequently and without clinical significance, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, Everolimus should be considered as predisposing patients to hemorrhage and potentially fatal should they develop severe drug-related thrombocytopenia.

Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with Everolimus in oncology clinical studies and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminases (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 (≤ 2.5 x ULN). Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer.

Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest of the patients had concurrent morbidities, which may have contributed to the reported events.

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo 2004). Sporadic cases of Hepatitis B reactivation have also been seen in this setting with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality (Loomba 2008). A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Hypophosphatemia, hypomagnesemia, hyponatremia, and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with Everolimus.

Table 4 provides general recommendations for the management of patients with suspected drug toxicities while on treatment with Everolimus as single-agent therapy.

More detailed information regarding Everolimus, reported suspected toxicities, and individual cases is provided in the [Investigator's Brochure].

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response and progression will be evaluated in this study using the international criteria by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI*, 92(3):205-216, 2000]. Changes in the largest diameter (uni-dimensional measurement) are used in the RECIST criteria. Note: lesions are either measurable or non-measurable using the criteria provided below:

12.2 Definitions

Measurable lesions: lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.

Non-measurable lesions: all other lesions (or sites of disease) including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions: all measurable lesions – up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs – should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions: all other lesions (or sites of disease) should be identified as *non-target lesions* and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

12.3 Guidelines for evaluation of measurable disease

All measurements should be taken and recorded in metric notation. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

12.4.3 Evaluation of Best Overall Response

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

12.4.4 Confirmation of Response

There will be no repeat imaging studies done solely for the purpose of confirming response. Patients will have follow-up imaging studies as outlined in the protocol and responses that are confirmed on follow-up scans will be noted.

12.4.5 Duration of Overall Response/ Progression Free Survival

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

Progression Free Survival will be calculated from the start of treatment until progressive disease or death. Patients who die before documented progression will be considered failures at their time of death. If the patient did not progress or die, the patient will be censored on the date of last follow-up.

13.0 CRITERIA FOR REMOVAL FROM STUDY

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Completion of treatment per protocol
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Inability of subject to comply with study requirements

If at anytime, the patient is found to be ineligible for the protocol as designated in the inclusion and exclusion criteria detailed in Section 6.0 (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

The purpose of this study is to assess the efficacy of Everolimus in patients with progressive urothelial cancer who have received prior cytotoxic chemotherapy. Historically, patients in this setting experience a median time to progression of 2-3 months (as illustrated in Section 3.1). Thus, the primary endpoint of this study will be the proportion of patients who are progression-free after two months on-study.

The sample size and stopping rules will be determined according to Simon's Minimax two-stage design. A two-month progression free survival rate of 50% would be considered not promising, while a 70% two-month PFS rate would be considered promising. In Stage 1 of the trial, 23 evaluable patients will be accrued to the study. If twelve or more patients demonstrate progression on imaging after two months on-study, the study will be terminated early and declared to have a negative result. If 13 or more patients are progression-free at two months, enrollment will be extended to accrue a total of 37 patients. If 24 or more patients are progression-free after their two-month scan (i.e. after Stage 2), the treatment will be declared effective and worthy of further testing.

Patients will be considered inevaluable for the primary objective (PFS at 2 months) if they receive ≤ one cycle of protocol therapy and are discontinued from protocol treatment for either rapid clinical deterioration related to progression of disease or adverse events unrelated to Everolimus. Patients with still be evaluable for toxicity assessment.
For the purposes of this study, the Type I (false acceptance of a non-promising therapy) and Type II (false rejection of a promising therapy) error rates have been set at 0.05 and 0.20, respectively. This statistical design would effectively discriminate between two-month PFS rates of <50% and >70% and yields **80**% probability of a positive result if the true two-month PFS rate is >70%. It yields 95% probability of a negative result if the true two-month PFS rate is <50%. The probability of early stopping under the null hypothesis is 66%.

The secondary endpoint of response rate will be estimated as the proportion of patients meeting the criteria outlined in Section 3.4.2.3 for a complete response or partial response.
This proportion will be reported along with its binomial confidence interval.

An accrual rate of 2-4 patients per month is anticipated, and thus the expected accrual time for the study will be approximately 10-20 months.

Frequency of toxicity will be tabulated according to the NCI Common Toxicity Criteria, version 3.0.

Biological markers including phospho-S6 and phospho-4E BP1 will be evaluated in all pre-treatment specimens. Patients will be categorized on the basis of marker levels into three categories: no expression, low expression, or high expression. These levels will be correlated with PFS using a log rank test and will be correlated with response to treatment (complete response/partial response versus no response) using Fisher's exact test..

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into the Clinical Research Database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be

monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials," which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org /irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees, *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.4 Protocol Amendments or Changes in Study Contact

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures

- Addition or deletions of a test procedure required for monitoring of safety

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval, but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- Changes in the staff used to monitor trials
- Minor changes in the packaging or labeling of study drug

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.3 Serious Adverse Event (SAE) Reporting

17.3.1 Serious Adverse Event (SAE) Reporting to the IRB

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event

- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.3.2 Serious Adverse Event (SAE) Reporting to Novartis

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

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of it's occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

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

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

Any pregnancy that occurs during study participation should be reported. To ensure patient safety, each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous

or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and newborn complications.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

A. Procedures and instructions

Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

Informed consent

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

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

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