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Division of Cancer Medicine

Everolimus versus Sunitinib Prospective evaluation in Non-clear cell renal cancer: A randomized phase II trial.

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1.1 OBJECTIVES

Primary

- To estimate and compare the progression-free survival (PFS) times of patients with advanced non-clear cell renal cell cancer (RCC) treated with everolimus or sunitinib as first-line therapy.

Secondary

- To assess the safety of everolimus and sunitinib in patients with advanced non-clear cell RCC.
- To estimate the overall survival (OS) times of patients with advanced non-clear cell RCC treated with everolimus followed by sunitinib, sunitinib followed by everolimus, or any single agent as part of this study.
- To estimate and compare the overall response rate (ORR) associated with each study drug given as first-line therapy in patients with advanced non-clear cell RCC.

2.0 BACKGROUND AND RATIONALE

Renal cell carcinoma comprises more than 90% of kidney cancer cases and accounts for approximately 2-4 % of all adult malignancies. In 2008, approximately 54,000 people in the United States were diagnosed with kidney cancer (renal cell cancer and transitional cell carcinoma of the renal pelvis) and approximately 13,000 died secondary to metastatic disease. Approximately 25 % of patients with RCC present with metastasis at the time of initial diagnosis and up to 20-30 % of patients develop recurrent disease after nephrectomy. Surgical removal of the primary tumor is the only effective therapy in the non-metastatic setting. No adjuvant therapy has been shown yet to alter the clinical course even in patients at high-risk for developing metastatic disease.

Metastatic RCC (mRCC) is a heterogeneous disease with variable clinical outcome. Two randomized phase III trials have provided support for performing cytoreductive nephrectomy in mRCC, although the most optimal timing of this procedure has not been determined. Some patients with solitary metastasis, who are candidates for complete metastasectomies, can achieve a long-term survival; however, once metastases develop in multiple organs, systemic therapies, until recently, have had little effect on the clinical course of the majority of patients. In an effort to objectively compare different therapies in the same trial, and similar therapies across trials, prognostic models have been developed to assign patients to different risk categories, based on pretreatment clinical features. Cytokines (interleukin-2, interferon alfa), which were the main therapy for mRCC for two decades, have recently been replaced by agents targeting the VEGF or the m-TOR pathways.

While conventional-type (clear-cell) RCC constitutes the majority of RCC cases, the rest of RCC cases belong to a heterogeneous group comprised of papillary, chromophobe, collecting duct carcinoma (CDC), renal medullary carcinoma, or unclassified.[6]

Sarcomatoid dedifferentiation may be associated with clear-cell RCC, papillary RCC and chromophobe RCC, and when present, it confers a worse prognosis. Clear-cell RCC is associated with mutation or silencing of the VHL tumor suppressor gene. This leads to upregulation of hypoxia-inducible factors (HIF) and to downstream upregulation of VEGF, resulting in increased angiogenesis, which is commonly noted in clear-cell RCC.[7] The identification of several key pathways relevant to RCC progression such as the VEGF pathway and the mTOR pathway has led to the development of several novel agents. The two tyrosine kinase inhibitors (TKIs), sorafenib and sunitinib, and the mTOR inhibitor temsirolimus received broad FDA approval for the treatment of advanced renal cell carcinoma[8], whereas everolimus received FDA approval for RCC patients previously treated with TKIs. After it garnered regulatory approval in Europe in combination with interferon alfa, bevacizumab is expected to be FDA approved in 2009.

Although the VEGF pathway has not yet been shown to be implicated in the development of RCC of non-clear cell histologies, there is evidence that proto-oncogenes involved in similar types of pathways do play a role. For instance, through investigation of a group of patients with hereditary papillary type 1 RCC, the c-met oncogene was identified. C-Met encodes the receptor for hepatocyte growth factor, part of a cell signaling cascade that is important for cell migration and differentiation and has been implicated in the development of a variety of cancers [9]. Subsequent studies in sporadic papillary RCC type 1 have shown that c-met is upregulated in some of these patients as well[10]. In chromophobe RCC, the BHD and c-kit genes have been implicated in tumorigenesis, however the pathways by which these genes work have not yet been clearly elucidated[11]. KIT was also found to be overexpressed in chromophobe as well as sarcomatoid RCC[12-13]. A recent study, based on tissue array conducted in clear cell RCC and papillary RCC, suggested that the VEGF pathway may be implicated in papillary RCC[14]. Jacobsen et al demonstrated no difference in VEGF expression as determined by immunohistochemical staining among papillary, chromophobe and conventional-type RCC[15].

Retrospective reviews indicate that the chromophobe and papillary subtypes have a better prognosis relative to other varieties of RCC. This reflects the fact that these tumors, if completely resected, are unlikely to recur. However, once these tumor types become metastatic, these histologies no longer confer benefit with the one exception to this rule being chromophobe, which has a more indolent course. In one retrospective study, the median overall survival of patients with metastatic papillary RCC and metastatic CDC was 5 months and 11 months, respectively. [6] A randomized trial using two interferon regimens showed a significantly shorter survival for patients with non-clear cell RCC compared to patients with clear-cell RCC.[7]

Currently, there is no established effective therapy for non-clear cell RCC. It has been difficult to assess the response of these less common RCC subtypes to therapy as most trials exclude them, and trials in which they are included do not report results separately from those with clear-cell histology. The available data suggests that these tumors are refractory to immunomodulation and cytotoxic therapy, which explains why traditional systemic therapy has been ineffective for this patient population.

Sunitinib malate, a multi-tyrosine kinase (MTK) inhibitor of VEGFR, PDGFR, FLT-3, and KIT, has produced significant tumor shrinkage in renal cell carcinoma. A recent retrospective review of patients with advanced papillary or chromophobe renal cell carcinoma treated with sunitinib or sorafenib showed a 17% response rate with sunitinib with median PFS time of approximately 8 months. A single-arm phase 2 trial of sunitinib in patients with non-clear cell RCC is currently completing accrual at our institution (41 patients accrued so far). So far, one patient achieved a partial response and several others achieved stable disease but the progression-free survival (PFS) was short compared with data generated in clear-cell RCC. A subset analysis of patients with non-clear cell RCC treated on a phase III trial showed improved survival with the mTOR inhibitor temsirolimus compared to IFN [8], lending support to investigate the role of mTOR inhibitors in non-clear cell RCC. Because there is no established effective therapy in non-clear cell RCC, there is an unmet need to develop therapy for this group of heterogeneous tumors. Therefore, it is important to evaluate the role of TKIs such as sunitinib and the mTOR inhibitors such as everolimus in a randomized phase II trial, with crossover design to allow patients to receive at progression the agent they did not receive upfront.

3.0 BACKGROUND DRUG INFORMATION

3.1 Sunitinib malate

Sunitinib malate (sunitinib; SU11248; SU011248; Sutent®) is a novel, multi-targeted, small molecule inhibitor of the receptor tyrosine kinases (RTKs) involved in tumor proliferation and angiogenesis, including vascular endothelial growth factor receptor-1 (VEGFR-1), -2, and -3, platelet-derived growth factor receptor PDGFRα and β , stem cell factor receptor (KIT), the tyrosine kinase (TK) receptor encoded by the *ret* proto-oncogene (RET; rearranged during transfection), and fms-like tyrosine kinase 3 (Flt3) (Investigator's Brochure SU011248, 2005). Sunitinib selectively and potently inhibits the class III and class IV split-domain RTKs (Mendel *et al*., 2003).

Sunitinib shows significant antitumor and antiangiogenic activity in a number of human tumor xenograft and angiogenesis models in mice as well as in phase 1 and 2 studies in patients with a variety of tumor types (Sakamoto, 2004). To date, over 3500 cancer patients have received sunitinib, including patients with renal cell carcinoma (RCC) and those with gastrointestinal stromal tumors (GIST). In phase 2 studies in cytokine-refractory metastatic RCC, sunitinib produced objective responses in 40% of patients with a median time to progression (TTP) of 8.7 months (Motzer *et al.,* 2006), while data from a phase 3 trial in patients with imatinib-resistant GIST indicate that sunitinib is highly superior to placebo ($p<0.00001$) with respect to time-to-progression (TTP) and overall survival (OS) (Demetri *et al*., 2005).

Sunitinib was granted approval on January 26, 2006 by Food and Drug Administration (FDA) for the treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate and advanced renal cell carcinoma (RCC). Approval for advanced renal cell carcinoma is based on partial response rates and duration of response.

Mechanism of Action:
Tumor VEGF expression has been associated clinically with disease prognosis in many different types of malignancies. VEGF expression is increased by diverse stimuli including proto-oncogene activation and hypoxia, with the hypoxic state frequently arising in solid tumors because of inadequate perfusion. In addition to its angiogenic role, VEGF also profoundly increases the permeability of the vasculature thereby potentially contributing to tumor progression. A leaky tumor endothelium enhances nutrient and catabolite exchange and represents less of a barrier to tumor cell migration and intravasation during metastasis. Two high-affinity receptors for VEGF with associated TK activity have been identified on human vascular endothelium, VEGFR-1/Flt-1 and VEGFR-2/kinase insert domain-containing receptor (KDR). Although the relative contributions of KDR and Flt-1 signaling in mediating tumor progression have not been elucidated, a number of studies suggest that KDR performs a predominant role.

In addition to VEGF receptor signaling, increasing evidence implicates PDGFR signaling in tumor angiogenesis. Recent nonclinical evidence suggests that inhibition of PDGFR signaling augments the antitumor and antiangiogenic effects of VEGFR inhibitors. In addition, PDGF signaling is implicated in the autocrine growth of tumor cells and in the recruitment and regulation of tumor fibroblasts.

Upon chronic oral dosing, sunitinib is expected to inhibit PDGF- and VEGF-driven angiogenesis and as a consequence, limit solid tumor growth. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, sunitinib treatment may have broad-spectrum clinical utility (Kim *et al*., 2004; Arora and Scholar, 2005). Sunitinib also exerts direct anti-tumor activity on cells that express target RTKs associated with tumor cell proliferation, such as KIT, PDGFR and RET. The clinical activity of sunitinib in patients with advanced GIST is an example of this anti-tumor effect.

3.1.1 Clinical Studies

Pharmacokinetics

Clinical pharmacology studies of sunitinib demonstrate that C_{max} and AUC increase in a proportional manner after single doses of 50-350 mg, as well as after multiple doses of 25-100 mg (Investigator's Brochure SU011248, 2005). C_{max} ranged from 26.0-48.7 ng/mL for the parent compound and from 4.3-8.9 ng/mL

for the major metabolite, SU12662. AUC_{0-24} ranged from 389-819 ng•hour/ml for sunitinib and 52-140 ng•hour/mL for SU12662. Peak plasma concentrations of the metabolite were much lower than those of sunitinib but declined more slowly. The terminal elimination half-lives of sunitinib and SU12662 are approximately 40 hours and 80 hours, respectively. After 28 days of dosing, the AUC_{0-24} for sunitinib increased 2.5- to 3.5-fold, while AUC_{0-24} of SU12662 increased 4- to 12-fold compared to day 1. Plasma concentrations of sunitinib and SU12662 typically reach steady-state levels after 1 to 2 weeks of dosing. Concentrations of parent drug and metabolite measured through 3 cycles of therapy have shown that C_{max}, AUC_{0-24}, and trough plasma drug concentrations during cycle 2 or cycle 3 were not increased above those observed in cycle 1.

The major *in vitro* studies on metabolism enzymology have been conducted in human liver microsomes, human hepatocytes, and expressed human CYP enzymes. Sunitinib is primarily metabolized in human liver microsomes by cytochrome P450 (CYP) isoform 3A4 but appears to have minimal potential to inhibit CYP3A4-mediated metabolism, and studies in human hepatocytes indicated that neither sunitinib nor SU12662 induced CYP3A4. These studies suggest that sunitinib and SU12662 are unlikely to have any clinically relevant drug-drug interactions with drugs that are substrates for CYP3A4. Concurrent administration of sunitinib and ketoconazole, a potent CYP3A4 inhibitor, resulted in less than a 2-fold increase in sunitinib exposure (based on C_{max} and AUC) and a small decrease in SU12662 exposure (Washington *et al*., 2003). However, concurrent administration of sunitinib and rifampin (a potent CYP3A4 inducer) in healthy male Caucasian and Asian volunteers resulted in a 4-fold reduction in sunitinib plasma exposure (AUC) and a 2.5-fold reduction in plasma C_{max} compared with sunitinib alone in both ethnic groups (Bello *et al*., 2005).

Scope of Clinical Program

To date, over 3000 patients with advanced malignancies have been treated with Sunitinib malate.

Multiple phase 1, 2 and 3 studies have been conducted or are underway. The primary dose limiting toxicity in phase 1 studies was fatigue/asthenia, which generally occurred 10 to 15 days after start of daily therapy, and was readily reversible upon discontinuation of Sunitinib malate treatment. Overall, the most frequent adverse events associated with Sunitinib malate treatment have been constitutional symptoms (fatigue/asthenia), gastrointestinal effects (nausea, diarrhea, stomatitis, dyspepsia), myelosuppression (eg, neutropenia, thrombocytopenia), and dermatologic effects (e.g., dermatitis, skin discoloration, hair depigmentation). Clinically significant neutropenia has been observed in very few solid tumor patients and febrile neutropenia has rarely been observed in this patient population. The degree of adverse event severity has correlated with higher drug exposure and/or lower patient performance status for both patients treated with previous chemotherapy and chemotherapy-naïve patients.

The maximum tolerated dose of Sunitinib malate using the Schedule 4/2 has been defined as 50 mg in Phase 1 clinical studies in patients with advanced solid tumors. Patients receiving this dose of Sunitinib malate achieved target steady state plasma concentrations of Sunitinib malate of greater than 50 ng/mL.

Clinically relevant Sunitinib malate antitumor activity has been demonstrated in Phase 1 patients with advanced malignancies, including patients with renal cell carcinoma, gastrointestinal stromal tumor, neuroendocrine tumor, sarcoma, thyroid cancer, melanoma and non-small cell lung cancer (NSCLC). In addition, a phase 2 study and a Pivotal study of Sunitinib malate in patients with cytokine-refractory metastatic renal cell carcinoma demonstrated a response rate of approximately 40% with a TTP of greater than 8 months compared to historical experience of less than 10% and 3 months respectively. A phase 3 study conducted in patients with malignant gastrointestinal stromal tumor (GIST) resistant to imatinib mesylate demonstrated a four fold improvement in TTP (1.5 mo to 6 mo) and a significantly improved OS. Preliminary data from an ongoing trial of Sunitinib malate monotherapy in patients previously pre-treated with a fluoropyrimidine, oxaliplatin and irinotecan for metastatic colorectal cancer have demonstrated a clinical benefit of approximatively 30% (CR+PR+SD for >6 months). Preliminary data from an ongoing Phase 2 study in patients with metastatic breast cancer indicate an approximately 15% ORR in following treatment failure with anthracyclines and taxanes.

Safety Profile

In studies evaluating starting doses that ranged from 75 to 100 mg daily, cardiac hypokinesis and clinical signs of congestive heart failure were reported in 4 of 62 advanced acute myeloid leukemia patients. The relationship to Sunitinib malate exposure was confounded by disease morbidities and prior anthracycline exposure. At the 50-mg dose level, asymptomatic decreases in cardiac ejection fraction have been observed in <5% of solid tumor patients, either with or without a prior history of cardiovascular disease or anthracycline exposure.

The most frequent adverse events (AEs) seen following sunitinib treatment are constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea, abdominal pain, anorexia, stomatitis, dysgeusia) and hematologic (neutropenia, thrombocytopenia) as well as skin discoloration (Investigator's Brochure SU011248, 2005). Most of the AEs are grade 1 or 2, but at 75 mg daily on an early phase 1 trial, grade 3 and 4 fatigue/asthenia were dose-limiting but readily reversible on discontinuation of treatment (Rosen *et al*., 2003). These investigators noted that the frequency and severity of AEs appeared to correlate with higher drug exposure or with lower performance status of the patients. In another phase 1 study, grade 3 fatigue and hypertension were dose limiting at 59 mg/m^2 and the MTD was defined as 42 mg/m^2 daily (Raymond *et al*., 2003). Tumor responses in patients treated at higher doses on this study were often associated with reduced intratumoral vascularization and central tumor necrosis which led to organ perforation in one patient and fistula in another. These

observations indicate the necessity for careful tumor density monitoring to detect early evidence of necrosis. Rapid destruction of bulky solid tumors can occur following sunitinib treatment, with pneumothorax, intestinal fistulae, or intestinal perforation each occurring at an incidence of less than 1.5% of patients. Across all patient populations, fatigue, hematologic AEs, and lipase elevations were the most common grade 3 and 4 events.

In addition to the frequent AEs noted above and those which are infrequent but severe, the following events have occurred: grade 2 edema and oral ulceration in AML (Fiedler *et al*., 2005); transient grade 3 and 4 hypertension, asymptomatic lipase increases (with or without amylase elevations), skin irritation in imatinib-resistant GIST (Desai *et al*., 2004); and grade 3/4 glossodynia in the NET trial (Kulke *et al*., 2005). Additional reports from the manufacturer include anemia, pyrexia, and dyspnea in AML; and abdominal pain, dyspepsia, skin discoloration, headache, constipation, dermatitis, increased lipase, limb pain, and taste disturbance in various solid tumor patients (Investigator's Brochure SU011248, 2005). Of interest, dyspepsia, dysgeusia, and stomatitis were reported twice as often in MRCC as in GIST, although these events occurred in both populations.

Many of the kinase inhibitors including sunitinib, sorafenib, imatinib, and the epidermal growth factor receptor (EGFR) inhibitors produce a variety of cutaneous side effects that, while not life-threatening, can be very troublesome to the patient (Robert *et al.*, 2005). As presented in this review, hair depigmentation, splinter subungual hemorrhages, acral erythema, and facial edema (occasional) are some of the dermatologic adverse effects seen with sunitinib. Because the severity of certain cutaneous effects appears to correlate with antitumor response in the case of the EGFR inhibitors, there is interest in further elucidating the mechanisms whereby kinase inhibitors produce these effects and in the potential for identification of predictive factors.

3.2 RAD001 (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.

At weekly and daily schedules and at various doses explored, everolimus is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

3.2.1 mTOR pathway and mechanism of action

At 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 lead 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 phospatase plays a 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). As 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).

3.2.2 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, concentrations capable of being reached in patients at the doses used in clinical trials.

Everolimus was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported (Zitzmann, et al 2007), as well as 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) and hepatocellular carcinoma cells (Sieghart, 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 fold 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 was 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, administred 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
- in 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)
- in 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 *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).

3.2.3 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 to be 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 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].

3.2.4 Clinical experience

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 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 the pharmacokinetics of everolimus.

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 in Black patients population pharmacokinetic studies have shown an average 20% higher clearance.

A high-fat meal altered the absorption of everolimus with 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 a 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

Appendix D lists examples of clinically relevant CYP3A inhibitors and inducers.

Please refer to Appendix D 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.

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 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].

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 4000 patients with various malignancies have been treated in either Novartis sponsored or non-Novartis sponsored, and 3 healthy volunteer clinical studies as of 31 Aug 2008. Overall, Novartis sponsored a total of 28 studies of everolimus administered either as single-agent (n=13), or in combination with other anti-tumor agents (n=15). 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 tumor, 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, randomized, double blind, placebo controlled study in patients with mRCC who progressed on a VEGFr TKI demonstrated that everolimus, administered daily at an oral dose of 10 mg, was superior to placebo for the primary endpoint of progression free survival. Median PFS was prolonged from 1.9 months for patients receiving placebo to 4.9 months for everolimus-treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.33, 95% CI 0.25-0.43, $p<0.001$) (Kay et al, 2009).

On 30 March 2009 everolimus was approved for use in the United States for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.
Overall, the most frequent adverse effects suspected to be related to everolimus have been stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus and dyspnea. The most common Grade 3 or 4 adverse reactions suspected to be related to treatment were anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gammaglutamyltransferase concentrations.

Non-infectious low-Grade (Grade 1/2) pneumonitis has led to development of treatment guidelines for the disorder (Table 3-2). The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia.

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

3.2.5 Everolimus Safety Profile

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, 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 9.4.1.

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 so that this aspect must be verified when interpreting results. For guidance on management of hyperlipidemia refer to Section 9.4.2.

Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results. For guidance on management of hyperglycemia refer to Section 9.4.2.

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 non-infectious/non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic. Advice on the management of pneumonitis has been provided in Table 4.

In oncology studies with everolimus, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and 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, and 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. Without clinical significance and infrequently, 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, 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 transaminase's (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 ($\leq$ 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 or the patients had concurrent morbidities, which might have contributed to the reported events.

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.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion:

1. Patients must have advanced non-clear cell RCC, which may include but is not limited to the following subtypes: papillary I or II, chromophobe, collecting duct carcinoma (CDC), translocation or unclassified. Patients with conventional-type renal cell carcinoma who have ≥ 20% sarcomatoid component in their primary tumor are eligible. Patients who have sarcomatoid features in FNA or core biopsy of any metastatic site are eligible, if they have an underlying renal cell carcinoma primary tumor.

2. Patients must have at least one measurable site of disease 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

3. ECOG performance status 0-1

4. Age ≥ 18 years

5. Patients must have adequate organ and marrow function within 14 days prior to study entry as defined below:

• Hemoglobin	≥ 9 g/dl (tx allowed)
• absolute neutrophil count	≥1,500/μL
• platelets	≥100,000/μL
• total bilirubin	≤ 1.5 mg/dl
• AST(SGOT) or ALT (SGPT)	≤2.5 X institutional uln, except in known hepatic metastasis, wherein may be ≤ 5 x ULN
• Serum Creatinine	≤ 1.5 x ULN (as long as patient does not require dialysis)

6. INR and PTT ≤ 1.5 x ULN within 14 days prior to study entry. Therapeutic anticoagulation with warfarin is allowed if target INR ≤ 3 on a stable dose of warfarin or on a stable dose of LMW heparin for > 2 weeks (14 days) at time of randomization.

7. Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN within 14 days prior to study entry.

8. Female patients of childbearing potential (not postmenopausal for at least 12 months and not surgically sterile) must have a negative serum or urine

pregnancy test within 14 days before study entry. Pregnancy test must be repeated if performed > 14 days before starting study drug.

9. Patients must give written informed consent prior to study entry, in keeping with the policies of each institution.

10. Patients with a history of major psychiatric illness must be judged (by the treating physician) able to fully understand the investigational nature of the study and the risks associated with the therapy.

11. Patients with controlled brain metastases are allowed on protocol if they had solitary brain metastases that was surgically resected or treated with radiosurgery or Gamma knife, without recurrence or edema for 3 months (90days).

4.2 Exclusion:

1. No other malignancies within the past 2 years except for adequately treated carcinoma of the cervix or basal (without recurrence post-surgery or post-radiotherapy) or squamous cell carcinomas of the skin.

2. No prior systemic therapy for RCC including prior adjuvant therapy, or investigational drug is allowed.

3. Patients currently receiving anticancer therapies or who have received anticancer therapies within 4 weeks (28 days) from enrollment into this study (including chemotherapy and targeted therapy) are excluded. However, patients are permitted to receive bisphosphonates. Also, patients who completed palliative radiation therapy prior to enrollment in this trial are eligible.

4. Patients, who have had a major surgery or significant traumatic injury (injury requiring > 4 weeks (28 days) to heal) within 4 weeks (28 days) 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 that may require major surgery during the course of the study.

5. Concomitant treatment with rifampin, St. John's wort, or the cytochrome p450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or Phenobarbital) or CYP3A4 inhibitors is not recommended on this study.

6. 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 defined as 0_2 saturation that is 88% or less at rest on room air
   - uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN
   - active (acute or chronic) or uncontrolled severe infections requiring antibiotic intervention
   - liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis

7. Patients must not have history of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of sunitinib or everolimus or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications.

8. Concomitant treatment with drugs with dysrhythmic potential (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended.

9. Patients receiving chronic, systemic treatment with corticosteroids or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.

10. Patients should not receive immunization with attenuated live vaccines within one week (7 days) of study entry or during study period.

11. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.

12. A known history of HIV sero-positivity.

13. Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus and/or sunitinib (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

14. Patients with an active, bleeding diathesis.

15. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Hormonal contraceptives are not acceptable as a sole method of contraception. (Women of childbearing potential must have a negative urine or serum pregnancy test within 7 days prior to study entry. Pregnancy test must be repeated if performed > 7 days before administration of everolimus and sunitinib)

4.3 Inclusion of Women and Minorities

This trial is open to women and men and members of all races and ethnic groups.

5.0 TREATMENT PLAN

5.1 Registration

This is a randomized phase II trial of sunitinib vs. everolimus in advanced non-clear cell renal cell carcinoma.

All patients will be registered in the approved Office of Research Administration (ORA) database at MD Anderson. For registration procedures for this protocol, please refer to Section 15.2 of the protocol and the Data Quality Management Plan (Appendix F).

5.2 Randomization and crossover design

Patients will be stratified by MSKCC risk grouping (Motzer et al, 2002) and histological RCC subtype (papillary vs. other non-clear cell subtypes), then they will be randomized (1:1) to receive everolimus or sunitinib. At disease progression, patients will be allowed to receive the agent that they did not receive upfront, i.e., patients who received sunitinib and had progressive disease will be treated with everolimus and vice versa. In most cases, treatment with the second agent will be initiated within 4 weeks (28 days) of completing the last dose of the first agent. In the case of patients receiving sunitinib after everolimus, patients have to wait 2 weeks (14 days) from the last dose of everolimus before they start treatment with sunitinib.

Note: Patients who develop progressive disease while receiving the 1st-line agent may receive radiation therapy or undergo surgery if indicated and continue to receive treatment on protocol, as long as the 2nd-line agent is commenced within 8 weeks from discontinuation of the 1st-line agent. Patients who develop toxicity necessitating discontinuation of the 1st agent may continue treatment on protocol but will cross over to receive the 2nd agent after recovery from the toxicity of the 1st agent.

We will use the Pocock-Simon minimization algorithm to ensure balancing with respect to treatment assignment over the stratification factors. We will balance treatment assignment with respect to the following stratification factors: Risk category (favorable intermediate poor); and histology (papillary versus other).

5.3 Data Collection

Data will be entered in the MD Anderson Genitourinary (GU) departmental oracle system. Registration data entry and randomization will occur prior to initiation of therapy.

5.4 Administration of Study Agent

The study drugs everolimus and sunitinib will be self-administered by the patients. The investigator will instruct the patient to take the study drugs exactly as specified in the protocol. Treatment must begin within fourteen days of randomization.

Everolimus will be administered orally as once daily dose of 10 mg. Patients will be instructed to take everolimus in the morning, at the same time each day.

Sunitinib will be taken orally as a once daily dose of 50mg on a 4-week (28 days) on, 2-week (14 days) off schedule.

5.4.1 Formulation and Packaging

Sunitinib will be obtained commercially as hard gelatin oral capsules containing 12.5mg, 25mg and 50mg equivalents of sunitinib. Please refer to the package insert for formulation and handling information.

Everolimus is formulated as tablets for oral administration of 10 mg and 5mg strength. Tablets are provided in blister-packs. Please refer to the package insert for formulation and handling information. Everolimus will be provided free of charge by Novartis.

Patients will continue taking everolimus or sunitinib until they have progressive disease or develop toxicity, then they will have the option of crossover to receive the agent they did not receive in the first-line setting.

5.5 Compliance

Patients will be required to return all empty bottles and blister packs of study medication at the beginning of every other cycle, for destruction. Patients will keep a drug diary to document administration compliance (Appendix H). The completed diaries will be brought to clinic for review.

5.6 Drug Storage and Drug Accountability (Everolimus only)

The investigator, or an approved representative, e.g. pharmacist, will ensure that all study medications are stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. All study

drug supplies must be kept in a locked limited access room. The study drug must not be used outside the context of this protocol. Everolimus will be stored at 15-30°C.

The investigator must maintain adequate records documenting the receipt, use, loss, or other deposition of the investigational product. The records must identify the investigational product, including batch or code numbers, and account for its disposition on patient-by-patient basis, including specific dates and quantities.

Unless otherwise instructed by Novartis in writing, our institutions will destroy any unused supplies of everolimus that expire during the term of this agreement, as well as all supplies that remain unused at the termination of this agreement. Institutions will destroy these materials in accordance with all applicable regulations, governmental guidelines, and institutional policies.

5.7 Concomitant Medications

Sutent
Caution is recommended when administering sunitinib with CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, erythromycin, clarithromycin) see examples in Appendix D, since these inhibitors may decrease sunitinib malate metabolism and increase sunitinib plasma concentrations. There is a mean 1.8-fold increase in exposure to sunitinib when sunitinib malate is co-administered with ketoconazole.

Substances that induce CYP3A4 activity may increase sunitinib metabolism and decrease sunitinib plasma concentrations. Co-administration of sunitinib and CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, Phenobarbital, St. John's wort) may significantly reduce exposure to sunitinib. Co-administration of sunitinib and rifampin decreased mean sunitinib 4-fold.

In addition, concomitant treatment with drugs with dysrhythmic potential (terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended.

Other concomitant therapies considered necessary for the patient's well being may be prescribed at the investigator's discretion as described below. Every medication including herbal supplements (e.g. St. John's wort) or treatment taken by the patient during the trial and the reason for its administration must be recorded in source documents and entered into the data collection system.

Everolimus
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. Surgery or radiation therapy for treatment of progressive disease is allowed (see Note in Section 5.2).
- Growth factors (e.g.G-CSF, GM-CSF, erythropoietin, platelets growth factors etc.) are not to be administered prophylactically but may be prescribed by the investigator for rescue from severe hematologic events, if this is thought to be appropriate.
- Concurrent administration of everolimus and strong CYP3A4 inhibitors (such as ketoconazole, itraconazole, ritonavir) and inducers (such as rifampin, rifabutin) should be avoided. Provided there is no alternative treatment available, patients should be closely monitored for potential toxicities.
- Concurrent administration of everolimus and moderate CYP3A4 inhibitors (such as erythromycin, fluconazole, calcium channel blockers, benzodiazepines) and moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin) should also be avoided if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of everolimus).
- Competitive inhibition could occur when everolimus is combined with drugs which are also CYP3A4 substrates. Therefore caution should be exercised in such cases.
- Co-administration with substrates, inducers, or inhibitors of P-glycoprotein should be avoided, if possible, or used subject to caution (e.g. increased frequency of safety monitoring, temporary interruption of everolimus).
- Grapefruit and grapefruit juice affect cytochrome P450 and P-glycoprotein activity and should therefore be avoided.
- In addition, patients should avoid Seville oranges and star fruit, as well as the juice of these fruits, which are potent CYP3A4-inhibitors.
- No chronic treatment with systemic steroids or another immunosuppressive agents. Topical or inhaled corticosteroids are allowed.
- Everolimus may affect the response to vaccinations making the response to the vaccination less effective. Live vaccines should be avoided while a patient is treated with everolimus.
  Oral anticoagulants such as warfarin are CYP2C9 substrates and, as such, no interaction with everolimus is expected. However, drug-drug interaction studies between macrolide antibiotics and warfarin have produced mixed

outcomes and the disparity in these findings has led to the conclusion that multiple factors may alter the clearance of warfarin. The 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).

5.7.1 Other Anticancer or Experimental Therapy

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biologic agents, hormone therapy or immunotherapy except for bisphosphonates. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

6.0 CORRELATIVE STUDIES (Optional procedures) MD Anderson Only

When feasible, pre-treatment tissue samples leftover from routine diagnostic procedures will be collected for the proposed correlative studies. In addition, residual pathological material may be collected for patients who undergo procedures while on therapy.

Specific biological markers will be assayed, focusing on factors associated with angiogenic signaling, and the activity and viability of specific cell types within the tumor, including the MAP kinase pathway, and the PI3K pathway with a focus on signaling molecules downstream of mTOR.

6.1 Epigenetic Analysis

Digital Restriction Enzyme Analysis of Methylation (DREAM) will be performed to obtain an overview of the aberrant methylated genes in patients with primary sensitivity and resistance to everolimus and sunitinib. DREAM data of healthy individuals is available. DREAM is a digital restriction enzyme analysis of methylation for quantitative mapping of DNA methylation with high resolution on the genome-wide scale. To perform the analysis, genomic DNA is sequentially digested with a pair of enzymes recognizing the same restriction site (CCCGGG) containing a CpG dinucleotide. The first enzyme, *Sma*I, cuts only at unmethylated CpG and leaves blunt ends. The second enzyme, *Xma*I, is not blocked by methylation and leaves a short 5' overhang. The enzymes thus create methylation-specific signatures at ends of digested DNA fragments. These are deciphered by next generation sequencing. Methylation levels for each sequenced restriction site are calculated based on the numbers of DNA molecules with the methylated or unmethylated signatures. The M. D. Anderson Epigenetics Center operates a Solexa core with the Illumina GA II machine that will be available for these studies. Genes of interest in this whole genome screen will be validated using DNA methylation analysis by bisulfite pyrosequencing. The expression of the pyrosequenced genes will be measured with quantitative RT-PCR using

LightCycler technology. The obtained results will be correlated with the response to treatment.

Particular emphasis will be put on PTEN and RASSF1. To reassess their expression in RCC samples, quantitative RT-PCR and immunohistochemical studies of these genes will be performed and will be correlated with the methylation status obtained by pyrosequencing. As the DREAM methods need to be applied in frozen tissues, we aim to identify potential predictive markers of response and resistance in the available frozen specimens, A validation of the potential predictive markers of sensitivity and resistance will be achieved by pyrosequencing of the paraffin-embedded specimens when available.

6.2 Gene expression analysis

We aim also to evaluate the potential effect of everolimus and sunitinib on the expression of TGF-α, which has been suggested to be a prognostic factor in RCC patients, and may increase RCC growth via an autocrine loop[17]. Oligonucleotide array analysis will also be performed to detect global patterns in pre-treatment tumor samples.

6.3 Immunohistochemical and immunofluorescence studies

A tissue microarray will be generated from nephrectomy or metastasectomy blocks from patients enrolled on the trial. For patients where blocks are not available selected staining may be performed on biopsy material where indicated. Specifically, to evaluate the MAP kinase and PI3K pathways, ERK, phospho ERK, p38, phospho p38, Akt phospho Akt, S6 kinase, phospho S6 kinase S6, phospho S6 and EIF4E and VEGF isoforms will be assayed using immunohistochemical techniques. In addition, p27 levels and its subcellular localization, Ki67 levels, and the TUNEL assay will be performed to evaluate the effect of everolimus and sunitinib on cell cycle, proliferation and apoptosis in endothelial, stromal and tumor cells. In addition, c-kit over-expression by immunohistochemistry will be assessed in patients with chromophobe RCC. Other biomarkers will be added as appropriate to contextualize the information gathered from the DREAM and the pyrosequencing analysis.

Moreover, we will assess the effect of everolimus and sunitinib on angiogenesis, endothelial FGFR, VEGFR2, Tie-2 and PDGFR levels and phosphorylation states will be assayed using coimmunofluorescence techniques.

Since chromosome copy number alterations have been shown to be associated with outcomes of clear-cell RCC, we will determine whether chromosomal imbalances identified with SNP arrays could be used as predictors of response to these agents. We will obtain archival FFPE tumor samples and extract DNA from the FFPE tissue sections for analysis with Affymetrix 250K Nsp SNP microarrays to identify genomic imbalances and loss of heterozygosity (LOH). SNP analysis will be performed at MDACC Sequencing and Microarray Facility (SMF).

6.4 Circulating endothelial cells

Venous blood (26ml) will be collected from patients to see if these tissue types can be used as surrogates for tumor tissue. Cellular biomarkers including circulating endothelial cells, circulating progenitor cells and molecular-target-expressing monocytic populations will be assessed by flow cytometry. A panel of vascular and inflammation-related cytokines including VEGF, FGF-2, sVEGFR-2, PDGF, and HGF among others will be assessed in plasma by the multiplex beads technology and/or ELISA. These circulating biomarker studies will be conducted by Dr. Shixia Huang, director of the Antibody-based Proteomics Core at Baylor College of Medicine.

Blood will be collected on day 1 of cycle 1, day 1 of all subsequent cycles, and at the end of treatment. Blood and tissue will be stored in the GU Biorepository.

6.5 Immunological Studies

Immunological studies will be conducted to define changes in effector and regulatory T cell populations and/or function and changes in cytokine profiles that occur after patients have started treatment. Laboratory techniques will follow previously published methods (Sharma et al., Cancer Immunity 2003; Sharma et al., J. Immunotherapy 2008; Gnjatic et al., Clinical Cancer Research 2009; Liakou et al., PNAS 2008; Tibes et al., Mol Cancer Ther 2006; Chen et al., PNAS, 2009) and will include flow cytometry, ELISA assays, ELISPOT assays, Affymatrix analyses, microRNA analyses, Western blot and reverse-phase protein array analyses. 90 cc of blood will be collected pre-therapy and at the time of administration of each dose of study drug. Blood will be processed by standard ficoll methods and immunological studies will be conducted on obtained PBMCs and plasma.

7.0 PRE-TREATMENT EVALUATION

7.1 Within 6 months (180 days) of study entry

- Doppler echocardiogram or MUGA scan for patients randomized to sunitinib

7.2 Within 28 days of study entry

- Signed and dated informed consent
- Physical Exam and updated medical history
- Updated evaluation of concurrent non-malignant diseases and recent medical therapy (within the thirty days prior to the evaluation).
- Imaging: CT scan of chest and abdomen (MRI of abdomen may be substituted). CT scan or MRI of the brain.
- CT scan of pelvis, plain films of bones/skeletal survey and bone scan will not be ordered routinely on all patients but only if clinically indicated
- 12-lead ECG

7.3 Within 14 days (+/- 3 days) of study entry

- Interim history
- Assessment of ECOG performance status, weight, temperature, blood pressure, heart rate, respiratory rate
- Physical Examination
- Laboratory testing: CBC with differential & platelets, chemistry panel including electrolytes (Na, K, Cl, CO_2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, INR/PTT, fasting lipid profile, fasting blood sugar, serum amylase and lipase, serum free T4 and TSH. For fasting blood sugar, patients should have nothing to eat or drink, except for water, for 8 hours leading up to the tests.
- Urinalysis
- Serum or urine pregnancy test for females of childbearing potential

7.4 Risk Grouping (MSKCC Prognostic Factors - see Appendix E) to be assessed within 14 days prior to randomization.

Risk Group: Good, Intermediate, or Poor

7.5 Treatment can not start until at least 1 week after any minor surgical procedure, excluding placement of a vascular access device and core biopsies.

8.0 EVALUATION DURING TREATMENT

8.1 A course of treatment is defined as 6 weeks (42 days +/- 4 days). The following must be performed on Day 1 of each course. All testing must occur within 3 days prior to dosing on all courses. If assessment and tests were completed within 7 days of Course 1 Day 1, procedures will not be repeated. Patients are required to come to the registering institution at the beginning of every course.

- Interim history
- Assessment of ECOG performance status, weight, temperature, blood pressure, heart rate.
- Physical examination
- Assessment of all concomitant medications and treatments taken since the last assessment.
- Assessment of adverse events and tumor-related signs and symptoms
- Assessment of treatment related toxicities
- Laboratory testing: CBC with differential & platelets, chemistry panel including electrolytes (Na, K, Cl, CO2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, fasting blood sugar
- Urinalysis.

- Fasting lipid profile for patients randomized to receive everolimus (nothing to eat or drink, except water, for 8 hours)

(Patients who have demonstrated stability on treatment can return to MDACC every 12 weeks for the above mentioned assessments and tests, at the discretion of the PI.)

- Doppler echocardiogram or MUGA scan every 24 wks (180 days) for patients randomized to receive sunitinib.
- Patients receiving sunitinib will have serum free T4 and TSH testing every other cycle (about every 12 weeks)

8.2 On days 15 and 29 (+/- 4 days) of course 1, all patients will be followed with vital signs (blood pressure and pulse only), CBC with differential & platelets, platelet count, electrolytes, BUN, creatinine, AST, ALT and total bilirubin. For patients randomized to receive everolimus, a fasting lipid profile should also be added. Day 15 and day 29 testing may be done locally.

8.3 Imaging scans (CT of chest and CT scan or MRI of abdomen) will be performed to determine disease response every 6 weeks (42 days)(+/- 4 days) for the first two cycles, then every other cycle [about every 12 weeks (84 days)], for as long as patients are receiving therapy on protocol. A follow-up CT scan of the pelvis will only be ordered if clinically indicated. A follow-up CT or MRI of the brain will only be ordered if clinically indicated.

8.4 On day 1 (+/-4 days) of each course, and at the end of treatment, blood will be collected for correlative studies (MD Anderson only) Patients who have demonstrated stability on treatment can return to MDACC every 12 weeks and have this sample collected, at the discretion of the PI.

8.5 Serum or urine pregnancy test will be repeated every 6 weeks (42 days +/- 4 days) while on-study for women of childbearing potential. Patients who have demonstrated stability on treatment can return to MDACC every 12 weeks and have this test completed, at the discretion of the PI.

8.6 End of Treatment Evaluation: Adverse events and tumor-related signs and symptoms will be assessed. For patients who develop toxicity related to study drug necessitating discontinuation of protocol therapy before restaging to assess tumor response, physicians treating these patients will make every effort to repeat the appropriate imaging studies if feasible and indicated to assess tumor response at the time the patients are taken off protocol treatment.

8.7 Long-term Follow-Up
Patients will be followed for survival every 6 months (180 days ± 1 month or 31 days) by record review or telephone correspondence.

STUDY CALENDAR

	Pre-Study	Course 1 (D15, D29) (+/- 4 days)	Day 1 of subsequent courses (+/- 4 days)	Every 12 weeks (84 days +/- 4 days)	End of treatment
Medical History	X[o]				
Physical Examination	X[p]		X		
Imaging	X[b,o]		X[b]	X[b]	X[l]
Weight, temperature, blood pressure, heart rate and respiratory rate	X[p]	X[j]	X		
CBC with differential & platelets	X[c,p]	X[c]	X[c]		
Chemistry Panel	X[d,p]	X[i]	X[d]		
Serum Free T4 + TSH	X[p]		X[e]	X[e]	
Urinalysis	X[p]		X		
Pregnancy Test	X[h,p]		X[h]		
Fasting Lipid Profile	X[p]	X[f]	X[f]		
Amylase and Lipase	X[p]				
Echocardiogram/MUGA	X[a,n]		X[a] 12-		
Lead ECG	X[o]				
ECOG Performance Status	X[p]		X		
Concomitant Medications			X		
Adverse Events			X		X
Long Term Follow Up					X[m]
Optional Procedures					
Blood			X[g]		X[g]
Tissue Sample	X[k]				

a. For patients randomized to sunitinib every 24 weeks (180 days). During Pre-Study, must be within six months of study entry.
b. CT scan of chest, CT scan or MRI of abdomen [every 6 weeks (42 days)(+/- 4 days)] for the first two cycles, then every 12 weeks (84 days)(+/- 4 days), and CT scan or MRI of the brain. CT scan of pelvis, plain films of bones/skeletal survey and bone scan will not be ordered routinely on all patients but only if clinically indicated; any follow-up CT scan or MRI will be ordered if clinically indicated.
c. Differentials include neutrophils, lymphocytes, monocytes, eosinophils and basophils
d. Includes electrolytes (Na, K, Cl, Co2), albumin, alkaline phosphatase, ALT, AST, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, glucose, INR/PTT (pre-study only)
e. Patients receiving sunitinib will have serum free T4 and TSH every 12 weeks (84 days) (+/- 4 days)
f. For patients randomized to everolimus
g. (+/- 4 days), and at the end of treatment
h. Only for women of childbearing potential, repeated every 6 weeks (42 days) while on study. May be serum or urine.
i. Only includes electrolytes, ALT, AST, total bilirubin, BUN, and creatinine
j. Only blood pressure and heart rate
k. Pre-treatment tissue sample leftover from routine diagnostic procedure.
l. For patients who develop toxicity related to study drug necessitating discontinuation of protocol therapy before restaging to assess tumor response, physicians treating these patients will make every effort to repeat the appropriate imaging studies if feasible and indicated to assess tumor response at the time the patients are taken off protocol treatment.
m. Patients will be followed for survival every 6 months (180 days ± 1 month or 31 days) by record review or telephone correspondence.
n. Within 6 months (180 days) of study entry
o. Within 28 days of study entry
p. Within 14 days (+/- 3 days) of study entry

9.1 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

9.1 Sunitinib Dose Modifications

Individual dose reductions will be permitted once a patient has experienced unexpected toxicity provided the criteria for patient withdrawal from study treatment have not been met. All individual dose reductions are relative to the lowest dose of the current cycle. Dose modifications may involve sunitinib in single decrements of 12.5 mg to a minimum dose of 25 mg. Dose modifications may involve everolimus in a single decrement of 5mg to a dose of 5 mg daily (dose level -1) or 5 mg every other day (dose level -2).

Table 1 describes the recommended dose modifications for sunitinib related toxicities:

Table 1 - Dose modifications for sunitinib malate associated Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level, or reduce the dose by 1 level at the discretion of the investigator*	Withhold dose until toxicity is grade ≤ 1 or has returned to baseline, then resume treatment at the same dose level, or reduce the dose by 1 level at the discretion of the investigator*
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is grade ≤ 2 or has returned to baseline, then resume treatment at the same dose level **	Withhold dose until toxicity is grade ≤ 2 or has returned to baseline, then resume treatment at the same dose level **

* Patients who develop grade 3 or 4 lipase or amylase without clinical or other evidence of pancreatitis, or grade 4 hyperuricemia or grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting and diarrhea must persist at grade 3 or 4, despite maximal medical therapy, to reduce the dose.

** Patients with recurrent grade 3 neutropenia or thrombocytopenia for > 7 days will dose reduce in the next cycle. Patients who develop grade 3 or grade 4 lymphopenia may continue study treatment without interruption.

Table 2 describes the recommended dose modifications for sunitinib related toxicities.

Table 2 - Sunitinib dose level modification guidelines

Dose level	**Dose and schedule**
0 (starting dose)	50 mg daily, 4 wks (28 days) on / 2 wks (14 days) off
-1	37.5 mg daily, 4 wks (28 days) on / 2wks (14 days) off
-2	25 mg, 4 wks (28 days) on / 2wks (14 days) off

9.1.2 Dose Re-Escalation

Doses reduced for drug related toxicity should generally not be re-escalated. However, individual re-escalation back to the previous dose level may be permitted provided the toxicity responsible for dose reduction has not recurred at a grade 2 for at least 4 weeks and with the agreement of the principal investigator of the study.

9.1.3 Overdose Instructions

In the event of an overdose, the PI and the manufacturers should be contacted to discuss the details of the overdose and formulate a clinical management plan. However, this contact will not delay patient care under any circumstance.

9.2 Everolimus Dose Modifications

Individual dose reductions will be permitted once a patient has experienced unexpected toxicity provided the criteria for patient withdrawal from study treatment have not been met. All individual dose reductions are relative to the lowest dose of the current cycle.

Table 3 describes the recommended dose modifications for everolimus related toxicities.

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 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, then interrupt everolimus until recovery to grade 1 or baseline, then resume treatment at the same dose level, or reduce the dose by 1 dose level at the discretion of the treating physician.
Grade 3 (except hyperlipidemia*) (except pneumonitis – refer to Table 5	Interrupt study drug until recovery to grade ≤2 then resume treatment at the same dose level, or reduce the dose by 1 dose level at the discretion of the treating physician. For pneumonitis consider the use of a short course of corticosteroids.
Grade 4	Discontinue everolimus.
Hematological toxicity	
Grade 2 Thrombocytopenia (platelets <75, ≥ $50x10^9$/L)	Interrupt study drug until recovery to grade ≤1 (>75 $x10^9$/L). Then reintroduce study drug at initial dose. If thrombocytopenia again returns to grade 2, interrupt study drug until recovery to grade 1 or baseline then resume treatment at the same dose level, or reduce the dose by 1 dose level at the discretion of the investigator.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 $x10^9$/L)	Interrupt study drug until recovery to grade ≤2 (platelets ≥ 75 $x10^9$/L), then resume treatment at the same dose level, or reduce the dose by 1 dose level at the discretion of the treating physician. If grade 3 thrombocytopenia recurs, discontinue study drug at the discretion of the treating physician.

Grade 4 Thrombocytopenia (platelets < 25 $x10^9$/L)	Discontinue study drug.
Grade 3 Neutropenia (neutrophils <1, ≥0.5 $x10^9$/L)	Interrupt study drug until recovery to grade ≤2 (neutrophils ≥ 1.5 x 10^9/L). Then resume treatment at the same dose level, or reduce the dose by 1 dose level at the discretion of the investigator. If ANC again returns to Grade 3, hold study drug until the ANC ≥ 1.5 x 10^9/L. Then resume study drug dosing at the lower dose level at the discretion of the treating physician. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 $x10^9$/L)	Interrupt study drug until recovery of ≥ neutrophils ≥ 1.0 x 10^9/L. Then resume study drug at the lower dose level at the discretion of the treating physician. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue study drug.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt study drug until resolution of fever and neutrophils ≥ 1.0 x 10^9/L. Then resume treatment at lower dose level at the discretion of the investigator. If febrile neutropenia recurs, discontinue study drug.
Grade 4 febrile neutropenia (life-threatening)	Discontinue study drug.
Any hematological or non-hematological toxicity requiring interruption for > 4 weeks	Discontinue study drug.

*Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies (see Sec. 3.2.5.2).

9.3 Monitoring of everolimus and sunitinib suspected toxicities

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 and/or sunitinib must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described below. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

9.3.1 Management of abnormal laboratory values

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to study drug must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. This may be done by telephone correspondence. 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.

9.3.2 Management of stomatitis/oral mucositis/mouth ulcers

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

1. For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.

2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol)** with or without **topical corticosteroids,** such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of metabolism of study drug, thereby leading to higher drug level 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.

Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 3.0.

9.3.3 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 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine 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, the affected patients had an abnormal fasting glucose at baseline. Based on this finding, it is suggested that optimal glucose control should be achieved before starting a patient on everolimus and should be monitored during everolimus therapy.

9.3.4 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). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. 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 modifications instructions are provided.

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.

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

9.3.5 Management of pulmonary embolism
Pulmonary embolisms confirmed by CT scan that are uncomplicated where medical intervention (anticoagulants) is indicated may be treated and stay on protocol at the discretion of the investigator.

10.1 CRITERIA FOR RESPONSE OR PROGRESSION

Evaluation of response will follow the Response Evaluation Criteria in Solid Tumors[18]. All tumor measurements must be recorded in centimeters.

- 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 (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum of longest diameters will be used as the reference by which the objective tumor response is characterized.

- Non-target Lesions:
  All other lesions (or sites of disease) up to five lesions per site and ten lesions in total 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.

Evaluation of Target Lesions:

- Complete Response:
  The disappearance of all target lesions.

- Partial Response:
  At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

- Progressive Disease:
  At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

- Stable Disease:
  Insufficient shrinkage to qualify for partial response, or insufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

Evaluation of Non-target Lesions:

- Complete Response:
  The disappearance of all non-target lesions.

- Incomplete Response/Stable Disease:
  The persistence of one or more non-target lesion(s)

- Progressive Disease:
  The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

- Evaluation of Best Overall Response: (see table below)

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Evaluation of Best Overall Response (RECIST)

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

CR= complete response; PR= partial response; SD= stable disease; and PD= progressive disease

11.1 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT

- Progressive disease: Patients, who develop rapidly progressive disease (clinically or by RECIST) before the scheduled evaluation every 6 weeks, may be taken off protocol treatment at the discretion of the investigator. Patients can continue to receive their assigned targeted agent, even if they develop progressive disease radiographically, as long as in the judgment of the treating physician, they are benefitting from their targeted agent.
- Intercurrent illness that prevents continuation of treatment.
- Unacceptable adverse event(s), or delay of treatment for > 4 weeks due to treatment-related toxicity. Note: Patients who require emergency surgery (e.g. for appendectomy or because of trauma complications) or who require a procedure (e.g. Kyphoplasty/vertebroplasty) may remain on trial, even if administration of the targeted agent is interrupted, as long as the targeted agent is resumed within 4 weeks from date of interruption.
- Patient non-compliance with therapy.
- Decision of the patient to withdraw from the study

11.1 Withdrawal from Study

A patient may be withdrawn from the study for any of the following reasons:

- adverse event(s)
- disease progression
- subject withdrew consent
- lost to follow-up
- death

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

12.1 SAFETY ASSESSMENTS AND REPORTING REQUIREMENTS

12.1 All patients will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by patients. An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. All adverse events encountered after the patient has provided informed consent and until 4 weeks after the patient has stopped treatment will be evaluated according to the NCI Common Toxicity Criteria (CTCAE) version 3.0. Prior treatment associated toxicities present at the time of

informed consent but before study treatment initiation, will be recorded as baseline abnormalities and graded according to CTCAE version 3.0 criteria.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and reported as described in the data submission schedule

A serious adverse event (SAE) is any adverse experience that results in any of the following outcomes: Death, a life-threatening adverse surgical experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Events *not* considered to be serious adverse events are hospitalizations for the purposes of this protocol and include:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event *not* fulfilling any of the definitions of serious given above and *not* resulting in hospital admission.
- Symptoms related to progressive disease such as bone pain will not be reported as toxicity or serious adverse events

Serious Adverse Events will be reported immediately to the MD Anderson Principal Investigator who will notify MD Anderson IRB per the IRB policy for reporting adverse events.

12.2 Reporting to Novartis (Everolimus only)

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring

- after the patient has provided informed consent and until 4 weeks after the patient has stopped study treatment/participation
- after the patient is randomized and until 4 weeks after the patient has stopped study treatment
- after the patient begins taking study drug and until 4 weeks after the patient has stopped study treatment

- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and until 4 weeks after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 4 weeks after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 4-week period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

The investigator must assess and record the relationship of each SAE to each specific study drug (if there is more than one study drug), complete the SAE Report in English, and send the completed, signed form by fax (888-299-4565) within 24 hours to the Novartis Clinical Safety and Epidemiology Department.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a Clinical Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Novartis instructions for rapid notification of serious adverse events
The MD Anderson 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 reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

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.

Pregnancies
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 the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

13.0 STATISTICAL CONSIDERATIONS / DATA ANALYSIS

This is a randomized, two-arm, parallel group, phase II trial for patients with advanced non-clear cell RCC. Patients will be randomized in a 1:1 scheme to receive either sunitinib (control arm) or everolimus (experimental arm). Patients must have advanced non-clear cell RCC, which may include, but is not limited to the following subtypes: papillary I or II, chromophobe, collecting duct carcinoma (CDC), translocation, or unclassified. Patients with conventional-type renal cell carcinoma who have ≥ 20%

sarcomatoid component in their primary tumor are eligible. Patients who have sarcomatoid features in FNA or core biopsy of any metastatic site are eligible, if they have an underlying renal cell carcinoma primary tumor.

Patients will be stratified as discussed above in section 5.2. Also, as discussed in section 5.2, at the time of disease progression or toxicity, patients will have the option to crossover to receive the agent they did not receive upfront.

For this randomized phase II study, we use a method advocated by Rubenstein et al for randomized phase II screening designs. In these screening designs, one conducts a direct, but non-definitive, "screening" comparison of the "experimental versus control treatments". Within this framework, we set the one-sided type I error rate to 0.05 and the power to 0.80.

The maximum sample size to be accrued is 108 patients. We estimate that 4 patients will be accrued per month. A total of 54 patients will be randomized to the sunitinib arm and 54 patients will be randomized to the everolimus arm. The primary measure of efficacy is PFS. **Note: patients who develop toxicity related to study drug necessitating discontinuation of protocol therapy before restaging to assess tumor response will not be included in the primary endpoint analysis of progression-free survival but will be included in the secondary endpoint analysis of time to failure.** Differences in PFS will be monitored at 3 time points and will take place as follows: 1) after 33 events (to monitor futility), 2) after 65 events, and 3) after at least 97 events occur. The test statistic used will be based on the log-rank test. An early stopping rule for futility will serve as guidance for early termination of patient accrual. The interim stopping rule consists of a group sequential test based on a Gamma family Type I error spending function. Results from the interim analysis will be reported to an independent Data Monitoring Committee (DMC) convened at MD Anderson Cancer Center. The DMC will assess the results along with supportive data including other efficacy outcomes, and safety data. It will use this data to possibly recommend early stopping or other study modifications.

Descriptive and inferential statistics will be used to summarize the treatment effects. The mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported for continuous variables by treatment group. For discrete (qualitative) outcomes, descriptive analyses will be based on the distribution of these discrete outcomes and will be reported as percentages and patient counts by treatment. Time to event endpoints will be descriptively summarized by Kaplan-Meier curves. Point and interval estimates of treatment effects will be based on maximum likelihood methods. For binomially distributed variables, we will report proportions, their 95% confidence intervals, differences in proportions and 95% confidence intervals for the difference in proportions. Confidence intervals will be constructed using two-sided 95% and will be based on the normal approximation. Although multiple secondary endpoints will be evaluated we will make no adjustment for multiplicities associated with these multiple tests.

13.1 Power, Sample Size and DMC Considerations

The statistical hypothesis is stated as:

$$H0: \quad \delta = 1$$
Versus
$$HA: \quad \delta < 1$$

where δ is the hazard rate for PFS (experimental versus control). Under the alternative hypothesis, the median PFS is 12 weeks for the control arm (sunitinib) and 20 weeks for the experimental arm (everolimus). We will use a GF group sequential test of futility (GF parameter equal to –3) calculated using EAST 5.0. Based on these assumptions, a 1:1 randomization between everolimus and sunitinib, and 2 interim futility looks when 33 and 65 events have occurred, one-sided α=0.05 and power=80%, the group sequential sample size requirement is 108 total patients.

The DMC will review the progress, efficacy, and safety profile of this study while it is ongoing. The committee will convene at the beginning of the study and at 2 interim time points (after 33 and 65 events have been observed). The test statistic used will be based on the stratified log-rank statistic. Stopping rules for futility will serve as guidelines for early termination of patient accrual. The interim stopping rule will consist of a group sequential test based on Gamma Family (GF) error spending functions with parameter value set to –3, (Hwang, Shih, and De Cani, 1990). We will stop for futility at the interim looks if the p-value is > 0.742 or > 0.3125 at the first and second interim looks, respectively.

13.2 Secondary Objectives

(1) Overall survival: Overall survival is calculated from the date of start of therapy to the date of death. Patients who are lost to follow-up will be censored at date of last contact.

We will use the Kaplan-Meier estimator to estimate the OS for each group of patients (control, experimental), and the log-rank statistic will be used to test for treatment differences. We will also use the Cox proportional hazards regression model to estimate the hazard ratio (experimental, control) for OS with 95% confidence intervals.

We will also assess the response rate and report 95% confidence intervals.

13.3 Additional analyses

Demographics: For each treatment group (control, experimental), summary statistics will be provided for age, baseline disease status and prior treatments.

Toxicity: Adverse effects that will be evaluated include, but are not limited to infections, renal toxicity, hepatic toxicity, and pulmonary toxicity. Methods of assessment will include monitoring blood counts, and performing laboratory tests as indicated by clinical signs and symptoms. Evidence of toxicity or adverse events will be recorded at all clinic visits. All observed adverse effects will be graded for all patients and the degree of association of each with therapy assessed. The incidence and severity of adverse events will be compared between the two treatment arms with Fisher's exact test.

13.4 Analysis of Circulating Endothelial Cells

These samples will be analyzed to complete the angiogenic profile of advanced renal cell carcinoma, in addition to the soluble protein (biomarker) evaluation.

Analysis of circulating endothelial cells will be reported by data tabulations, descriptive statistics, and graphical presentations and as appropriate in relation to clinical response and pharmacokinetic endpoints.

14.0 DATA AND PROTOCOL MANAGEMENT

Protocol Compliance: All required interim and pretreatment data should be available, and the physician must assess tumor response and must provide a detailed description of toxicity, when appropriate. If dose modifications or treatment interruptions are necessary, the details must be carefully documented. Performance status must be documented at each toxicity assessment.

Data Capture: Data will be entered in the MD Anderson GU departmental oracle system. Registration data entry and randomization will occur prior to initiation of therapy. All eligibility criteria must be satisfied.

Accuracy of Data Collection: The MD Anderson Principal Investigator will be the final arbiter of response and toxicity, should a difference of opinion exist.

14.1 Schedule of Data Submission

MD Anderson protocol specific Case Report Forms and/or electronic Case Report Forms will be used for collection of all study data. The schedule for submission of case report forms and pertinent source documents to MD Anderson is as follows:

Case Report Forms/Source Documents	Schedule for Submission
Informed Consent/Patient Authorization for the Release of Personal Health Information	Prior to study registration
Eligibility Checklist	Prior to study registration
On-Study Form Supporting Source Documents (e.g. Pathology reports, Medical Administration Records, Radiology/Laboratory Reports, History and Physical, Progress Notes)	14 days after treatment initiation
Chemotherapy/Treatment by Cycle Form (Chemotherapy, Laboratory Results, Concomitant Medications) Supporting Source Documents	14 days after cycle completion
Adverse Event Form Supporting Source Documents	14 days after cycle completion
Response Assessment Forms (Disease Measurements) Supporting Source Documents	14 days after protocol defined imaging assessment
Off Treatment Supporting Source Documents	14 days after last treatment date
Survival Update Form Supporting Source Documents	14 days after protocol defined survival review
Off Study Form Supporting Source Documents	14 days after patient removed from study

15.0 MULTICENTER PROCEDURES

Participating multicenter institutions will follow the guidelines as addressed below, in the MD Anderson Multicenter Management Plan (Appendix F), and throughout this protocol.

15.1 Principal Investigators

The principal investigator(s) will be responsible for the conduct of the study and monitoring its progress. The responsibility for all reports and data required by MD Anderson will be that of the principal investigator(s).

15.2 Centralized Patient Registration and Randomization

Patients who are candidates for the study will first be evaluated for eligibility by the local investigator. All patients will be registered by designated research staff in the GU department.

All multicenter patients must be registered both locally and centrally with MD Anderson.

At the time of registration, participating institutions will be required to submit a completed and signed eligibility checklist and informed consent document. No additional source documentation will be required for patient registration.

15.2.1 Eligibility Exceptions

All exceptions to eligibility must first be approved by the Protocol Chair with appropriate rationale following MD Anderson guidelines. If eligibility clarifications are required from participating institutions, all eligibility questions should be routed to the MD Anderson GU Department in order to document the question and Protocol Chair response.

15.3 Guidelines for Reporting Participating Site Serious Adverse Events to MD Anderson:

Any Serious Adverse Event (SAE) will be reported to the MD Anderson GU Department within 24 hours of knowledge of the event. The participating institution will submit the SAE to its own IRB according to institutional policy and must forward a copy of the report to MD Anderson within 5 calendar days. The MD Anderson GU department will submit participating site SAE reports to the MDACC IRB and Novartis.

SAE notifications and reports will be submitted to:

Fax or email a completed SAE Form to:

MD Anderson GU Department (notifications and reports)
Attn: 2009-0628
Fax: 713-563-0857
Email: GU2009-0628@mdanderson.org

MD Anderson will maintain documentation of all Serious Adverse Events from each institution. MD Anderson will notify all investigators of any serious and unexpected adverse experiences that are possibly related to the study therapy. The investigators are to file a copy in the protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

15.4 Guidelines & Procedures for reporting Violations, Deviations and Unanticipated Problems.

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol deviations, violations, and unanticipated problems. The Protocol Chair will also be responsible for ensuring that all protocol deviations, violations, and unanticipated problems are reported to the MD Anderson IRB per MD Anderson institutional guidelines.
Participating Institutions: Protocol deviations, violations, and unanticipated problems occurring at a participating institution will be submitted to that institution's own IRB. A copy of the participating institution's IRB deviations, violations, and unanticipated problems report will be forwarded to MD Anderson by facsimile or via email within 7 calendar days after the original submission.

15.4.1 Definitions

The definitions for protocol violation and deviation as described by the MD Anderson IRB will be applied for reporting purposes for all institutions participating in the trial.

Protocol Deviation: Noncompliance with the protocol that does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data. Deviations may be caused by the action of the subject, the investigator, the research staff, or natural events.

Protocol Violation: Changes to protocol procedures without prior approval of the IRB/Sponsor. Violations may significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity and adversely affect patient's safety and rights.

Unanticipated Problems: An incident, experience or outcome, that is unexpected, related or possibly related to participation in the research and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized. These incidents do not meet the definition of an adverse event. Unanticipated problems are not limited to study participants, and may also include others such as family members and research staff.

MD Anderson GU Department: Upon receipt of the violation/deviation/unanticipated problem report from the participating institution, the Protocol Chair will review and submit the report to the MD Anderson IRB for review.

15.5 Research Team Teleconferences

The MD Anderson and participating institution's PIs and study teams will participate in teleconferences as needed to discuss the following information:

- Status of patients enrolled at sites including
  - Eligibility for trial
  - Status of treatment
  - Adverse Events
  - Response evaluation
  - Any questions or concerns

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