A Phase II Trial of Everolimus and Bevacizumab in Advanced Non-clear Cell Renal Cell Cancer (RCC).

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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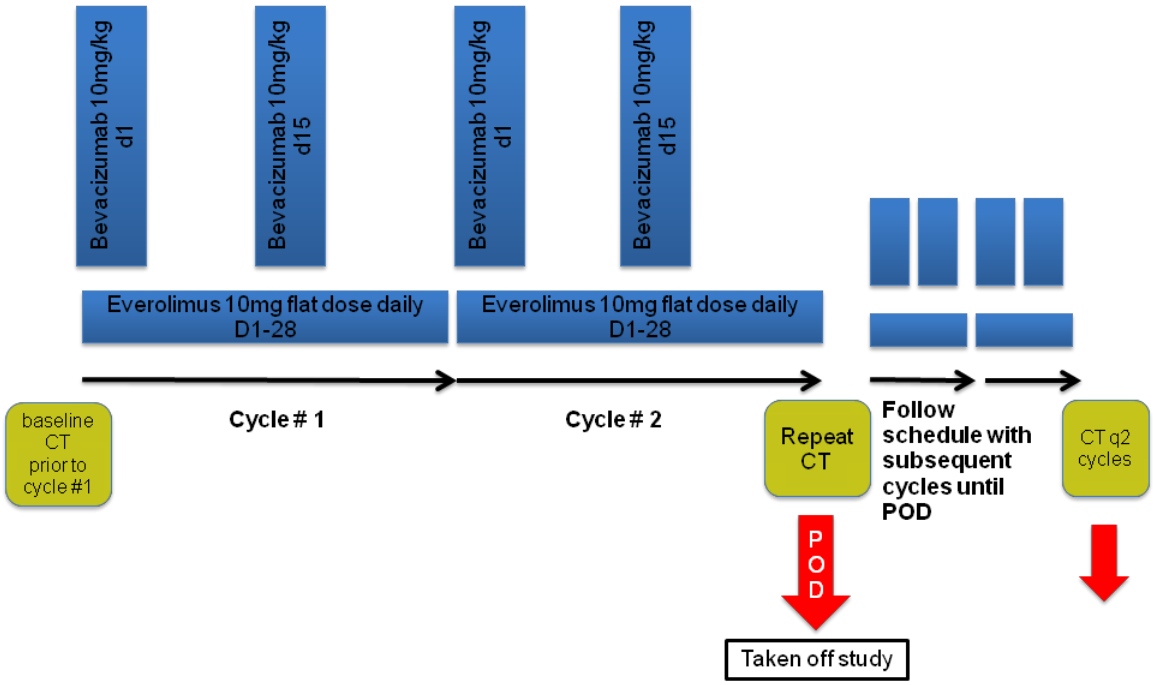
1.1 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single institution open-label phase II trial of everolimus and bevacizumab in patients with advanced non-clear cell RCC, who have not received prior VEGF-.or mTOR-targeted therapy. Primary endpoint will be progression free survival (PFS) after six months of treatment, secondary endpoints will be objective response rate (ORR) per RECIST 1.1 (Eisenhauer, Therasse et al. 2009), and safety of this drug combination in the study population. Explorative endpoints will include correlation of pretreatment tissue biomarkers with treatment response.

1.2 Study Schema



2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To evaluate the efficacy of combining everolimus and bevacizumab in patients with advanced RCC of non-clear cell histology
  - The primary endpoint in this study will be the percent of patients alive and progression-free after 6 months of therapy.
  - Secondary endpoint will be the overall response rate (ORR) per the international criteria defined by the Response Evaluation Criteria in Solid Tumors Committee (RECIST 1.1).

Secondary objectives:

- To investigate the safety of everolimus and bevacizumab in patients with advanced RCC of non-clear cell histology.
  - Toxicity will be assessed using Common Terminology Criteria for Adverse

Events (CTCAE) v4.0 (Gompertz 1825), as outlined in section 11.5. Toxicities will be summarized by type and grade using frequencies and rates.

- To determine whether relevant biomarkers in tumor tissue can be predictive of treatment response.
- To obtain data regarding efficacy of everolimus and bevacizumab in patient with non-clear cell renal cell cancer types with papillary features.

3.1 BACKGROUND AND RATIONALE

3.1 Epidemiology

Renal cell carcinoma (RCC) is the most common malignancy of the kidney, and is expected to account for more than 58,000 new diagnoses of cancer and over 13,000 cancer deaths in the United States during 2010 (Jemal, Siegel et al. 2010). Annual incidence and mortality worldwide are estimated over 270,000 and 116,000, respectively (Ferlay, Shin et al. 2010). Incidence is rising, and RCC now make up 3.8% of new cancer diagnoses in the United States (Jemal, Siegel et al. 2010). It is more common in men than women with an approximate incidence of 1.5:1. Metastatic RCC occurs in approximately 30% of the newly diagnosed patients, with 1.5 to 3.5% having a solitary metastasis (Flanigan, Salmon et al. 2001).

3.2 Subtypes of RCC

RCC is a heterogeneous disease, comprised several different histological types with distinct genetic alterations, varying clinical course, and variable responsiveness to systemic therapy. The current classification of RCC is based on the Heidelberg system, which identifies several distinct malignant histologic subtypes of RCC including clear-cell, papillary, chromophobe, collecting-duct (Bellini duct) with its variant medullary type carcinoma, and unclassified RCC (Kovacs, Akhtar et al. 1997). The most common subtype is clear cell RCC (60–80%), often termed conventional RCC. The remaining subtypes are often grouped as non-clear cell RCC (NCRCC) and differ in their incidence with the order being papillary (7–14%), chromophobe (6-11%), unclassified tumors (3-5%), and collecting duct RCC (<1%) (Kovacs, Akhtar et al. 1997; Reuter and Presti 2000). Sarcomatoid features can be seen in all different subtypes of RCC and typically confer a more aggressive course with adverse outcome. This is thought due to the de-differentiation of the original epithelial malignancy (Bertoni, Ferri et al. 1987; Mai, Landry et al. 2001; Kourda, Zeddini et al. 2006).

The prognostic significance to histologic subtype has been intensely studied. Several retrospective studies have suggested that stratification by histologic subtype can lend prognostic value (Moch, Gasser et al. 2000; Amin, Tamboli et al. 2002; Cheville, Lohse et al. 2003).Different implications have been reported for localized and metastatic disease. Favorable prognosis after nephrectomy for a localized primary tumor has been seen in papillary and chromophobe cell types compared with the clear-cell type (Moch, Gasser et al. 2000; Amin, Tamboli et al. 2002; Cheville, Lohse et al. 2003; Beck, Patel et al. 2004). In

metastatic disease, non-clear cell histologies have been reported to portend poor survival compared to conventional RCC in univariate analysis. Better outcomes have been cited for patients with chromophobe tumors than for those with metastatic collecting duct or papillary RCC (Motzer, Bacik et al. 2002). This was not confirmed by a more recent international multicenter retrospective analysis of >4000 cases (Patard, Leray et al. 2005), which noted no significant survival difference among clear-cell, papillary and chromophobe RCC when adjusting each histologic subgroup for TNM stage (including Stage IV disease) in multivariate analysis. The only exception was chromophobe histology, which resulted in better outcome only in high grade tumors (nuclear grade 3 and 4 tumors) (Patard, Leray et al. 2005).

3.3 Therapy of metastatic RCC

RCC is characterized by a high degree of resistance to chemotherapy. Interferon alfa-2a (IFN) and interleukin-2 were standard therapies for patients with metastatic RCC. Both achieve complete plus partial responses in 10% to 20% of patients, only a minority of treated patients experiences a favorable response, and few achieve long-term survival (Fyfe, Fisher et al. 1995; Fossa 2000). While these treatments were not prospectively evaluated in NRCC in dedicated trials, retrospective data suggested inferior outcome for patients with NRCC compared to conventional RCC (Motzer, Bacik et al. 2002).

More recently, targeted agents blocking the (Yang, Haworth et al. 2003)vascular endothelial growth factor (VEGF) pathway or the mammalian target of rapamycin (mTOR) have emerged as powerful tools in the management of advanced disease and have become the standard of care in conventional RCC. It is important to note that the majority of Phase III clinical trials have predominantly enrolled patients with clear-cell histology.

3.3.1 The VEGF-pathway and RCC

Angiogenesis, or new blood vessel formation, is critical to tumor growth, invasion, and metastasis (Posada, Gulley et al.). Several humoral factors stimulate angiogenesis. These factors act either by inducing the enzymatic breakdown of the perivascular basement membrane or by inducing proliferation and chemotaxis of endothelial cells. Both components are critical for successful neovascularization, and the inhibition of either arm has been hypothesized as having a potential antitumor or antimetastatic effect on malignant cells. Vascular endothelial growth factor (VEGF) is a 43- to 46-kd glycoprotein that induces the proliferation and migration of vascular endothelial cells (Rudloff, Boulay et al.). These activities are mediated via the two receptors for VEGF, flt-1 and KDR, which are found predominantly on vascular endothelial cells (Rudloff, Boulay et al.). In preclinical models, VEGF is a potent neovascularization agent for both normal and malignant microvasculature (Smeraglia).

Many malignant cells produce VEGF, which serves as an autocrine factor for the induction of neovascularization. Several studies have demonstrated a correlation between high levels of VEGF and increased risk of metastatic disease and overall poor prognosis in a variety of malignancies including non–small-cell lung cancer and other cancers. In addition, increased expression of VEGF by malignant tumors is associated with a more invasive phenotype

(Steinbild, Baas et al. ; Higuchi, Fockler et al. 193). In preclinical animal models, the inhibition of VEGF was found to be associated with stabilization of established tumors (Cheung, Morley et al. 199). The use of anti-VEGF antibodies has been extensively studied in preclinical in vivo models and has demonstrated an inhibition of tumor growth in a dose-dependent manner (Miller, Burstein et al.).

Advances in understanding the biology and genetics of RCC have led to major therapeutic implications. The discovery of the von Hippel-Lindau (*VHL*) gene and its role in regulating pro-angiogenic factors including VEGF, platelet-derived growth factor (*PDGF*), and others provided potential targets for novel agents (Choueiri, Bukowski et al. 2006). In clear cell RCC, VEGF targeted therapies, both receptor tyrosine kinase inhibitors (TKI) (sunitinib, sorafenib) and VEGF-A ligand antibodies (bevacizumab), were shown to have activity in the metastatic setting (Awada, Hendlisz et al. 2005; Motzer, Michaelson et al. 2006). However, *VHL* inactivation in RCC is almost exclusively seen in patients with clear cell histology (Gnarra, Tory et al. 1994). Despite this, tumor samples from patients with NCRCC can demonstrate high expression of VEGF (Jacobsen, Grankvist et al. 2006), making VEGF-targeted therapy an attractive therapeutic option. The mTOR pathway has been implicated as a major contributor through an autocrine loop involving VEGF, described in further detail below.

3.3.2 VEGF targeted Tyrosine Kinase Inhibitors (TKI) in RCC

The oral multi TKI Sunitinib demonstrated a progression-free survival (PFS) benefit over interferon alpha in a phase 3 pivotal trial, 11 months (95% CI 10-12) versus 5 months (95% CI 4-6) (Motzer, Hutson et al. 2007). PFS benefit was also demonstrated in a phase III trial comparing sorafenib, another oral TKI, to placebo (Escudier, Eisen et al. 2007). These pivotal studies were exclusively performed in patients with clear cell histology. Both drugs have been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic RCC. The third approved oral TKI in RCC is pazopanib, which was tested in a multicenter randomized placebo-controlled phase 3 trial in both treatment naïve and cytokine pretreated patients (Sternberg, Davis et al. 2010). ORR was 30% for pazopanib compared with 3% for placebo; PFS was significantly prolonged in the overall group (median PFS 9.2 months) as well as the treatment naïve population (median PFS 11.1 months).
The role of VEGF targeted TKI is less clear in NCRCC. A retrospective multicenter review published by Choueiri and colleagues looked at 41 patients with advanced papillary and chromophobe RCC (Choueiri, Plantade et al. 2008). In papillary RRC patients, response rates were low (5%; two responders, both received sunitinib), PFS appeared longer in patients treated with sunitinib compared to sorafenib (11.9 vs 5.1 months, $p<0.001$). In chromophobe RCC, results were more encouraging with RR of 25% and median PFS more promising in sorafenib than sunitinib (27.5 vs 8.9 months, respectively).
Prospective data for sunitinib and sorafenib in NCRCC is limited. French investigators presented preliminary results of a Phase II study of sunitinib in advanced type I and II papillary RCC (Ravaud, Oudard et al. 2009). In type II papillary RCC one of 23 patients (4%) achieved a Partial Response (PR), four patients (17%) had Stable Disease (SD) for 12 weeks or more, five (22%) had progressed at the time of initial evaluation on treatment. Of

five patients with type I papillary RCC none had a PR, three (60%) had SD; the remaining patients had not been evaluated at the time of report.

Similarly, investigators from M.D. Anderson and Fox Chase Cancer Center presented their phase II data for 23 patients with advanced papillary RCC treated with sunitinib at the 2010 annual ASCO meeting (Plimack, Jonasch et al. 2010). There were no major responses. Eight pts had stable disease as best response. The radiologically assessed 6-month PFS rate was 0.34 (95% CI, 0.18- 0.63); median PFS was 1.6 months (95% CI, 1.3-12), median Overall Survival (OS) 10.8 months (95% CI, 6.2-NE). Recent data from our own institution includes a single-institution phase II study of sunitinib in patients with metastatic non-clear cell RCC (Molina, Feldman et al. 2010). Twenty three patients were enrolled. All patients received sunitinib 50 mg administered orally for four weeks followed by two weeks of rest (4/2). Overall, there was only one objective response (4%) in a patient with unclassified RCC: Sixteen (70%) had stable disease (SD) and six (26%) progressive disease (PD) at their first assessment. The median PFS was 5.5 months. With similarly disappointing results, these studies all suggest inferior benefit for sunitinib when compared to historical controls in conventional RCC, where robust objective responses are typically seen.

3.3.3 VEGF targeted monoclonal antibody therapy in RCC - Bevacizumab

Bevacizumab (rhuMAb) is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) *in vitro* and *in vivo* assay systems. Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis.

The overall safety profile of bevacizumab is based on several phase III trials treating patients with various malignancies such as colorectal cancer, non-small cell lung, breast cancer, ovarian cancer, and renal cell cancer, as well as patients with various other advanced malignancies in early phase trials, who received bevacizumab either as a single agent or in combination with chemotherapy in clinical trials. Throughout these studies, bevacizumab has generally been found to be well-tolerated, with the primary toxicities being hypertension (occurrence of grade 3/4 hypertension ranging from 2 to 16% in various studies) and proteinuria (1 to 2 % in colorectal cancer trials). Less frequently, it causes albuminuria, occasionally complicated by the nephrotic syndrome. Bevacizumab is also known to increase the risk for venous as well as arterial thromboembolic events, bleeding and disturbed wound healing, impairment of cardiac function, as well as stroke and myocardial infarction. In rare cases, gastrointestinal perforation, anastomotic dehiscence and pulmonary hemorrhage have been reported.

The phase III multicenter double-blind AVOREN trial of bevacizumab plus interferon vs. interferon alone enrolled 649 patients with untreated advanced RCC and either clear-cell only (87% of patients) or mixed histologies (>50% clear cell, 13% of patients) (Escudier, Pluzanska et al. 2007). The trial demonstrated superiority to the bevacizumab arm with significantly longer PFS of 10.2 months vs 5.4 months in the interferon alone arm and higher

ORR (31% and 13%, respectively, p=0.0001). The primary endpoint for this study was OS, and only a nonsignificant trend towards improvement was seen in the final survival analysis (median OS 23.3 months and 21.3 months, respectively, p=0.336) (Escudier, Bellmunt et al. 2010). It was however noted that the majority of patients in both arms received at least one post protocol antineoplastic therapy, likely confounding the OS analysis.

649 patients were treated in this study in 18 countries. Patients receiving bevacizumab and interferon-alfa experienced the following Grade 3/4 adverse events: fatigue 12%, asthenia 10%, proteinuria 7%, neutropenia 4%, and bleeding, hypertension influenza-like-syndrome, anorexia, anemia (all 3% each).

Table 3.1 – Selected grade 3 / 4 adverse events from phase III study of bevacizumab and interferon in RCC (Escudier, et. al (Escudier, Pluzanska et al. 2007))

	Number of patients (%)	
Adverse event	IFN + placebo (n=304)	IFN + Bevacizumab (m=337)
Any grade 3/4 adverse event	137	303
Fatigue/ asthenia/malaise	46	76
Proteinuria	0	22
Hypertension	2	13
Hemorrhage	1	11
Venous thromboembolism	2	6
Gastrointestinal perforation	0	5
Arterial ischemia	1	4

As mentioned above, AVOREN included 13% patients with mixed histologies, i.e. with non-clear cell component of <50%. An unplanned secondary analysis of the AVOREN data evaluating specifically this subgroup of patients was presented at the 2008 ASCO meeting (Escudier, Ravaud et al. 2008), and although patients with mixed histologies had poorer PFS than those with pure clear-cell RCC, the combination of bevacizumab plus interferon produced better results than interferon alone in the mixed-histology group (5.7 vs 2.9 months; HR, 0.53; P<.007). The authors concluded benefit to bevacizumab, irrespective of tumor histology.

A second Phase III study conducted and analyzed by the Cancer and Leukemia Group B (CALGB) in advanced clear cell RCC confirmed superiority of bevacizumab in combination with interferon over interferon alone (Pollack, Perou et al. 199). The median PFS was 8.5 months in patients receiving bevacizumab plus IFN (95% CI, 7.5 to 9.7 months) versus 5.2 months (95% CI, 3.1 to 5.6 months) in patients receiving IFN monotherapy (log-rank P < .0001). The adjusted hazard ratio was 0.71 (95% CI, 0.61 to 0.83; P < .0001). Bevacizumab plus IFN had a higher ORR as compared with IFN (25.5% [95% CI, 20.9% to 30.6%] v 13.1% [95% CI, 9.5% to 17.3%]; P < .0001). Overall toxicity was greater for bevacizumab plus IFN,

including significantly more grade 3 hypertension (9% v 0%), anorexia (17% v 8%), fatigue (35% v 28%), and proteinuria (13% v 0%). No new safety signals related to interferon and bevacizumab were observed (Pollack, Perou et al. 199).

3.3.4 Bevacizumab - pharmacokinetics / pharmacodynamics

In phase 1 testing, bevacizumab had a low toxicity profile in most patients with no dose-limiting toxicity observed at doses ranging from 0.1 to 10 mg/kg (Norden-Zfoni, Manola et al.). Treatment did not induce antibodies to bevacizumab. Terminal elimination half-life was approximately 21 days. Free serum VEGF concentrations were found to be reduced and, at doses of 0.3 mg/kg, were below the detectable limit of the assay after the administration of bevacizumab and remained undetectable for the duration of the study (Norden-Zfoni, Manola et al.).

3.3.5 The mTOR pathway and cancer

The mammalian target of rapamycin (mTOR) is 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 (Schwab, Christensen et al. 1987). mTOR is downstream the 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 (Schwab, Christensen et al. 1987; Bjornsti and Houghton 2004):

- 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 et al. 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, Harris et 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, which is not upstream of mTORC1. PHLPP phosphatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton (Wullschleger, Loewith et al. 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, Geyer 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).

3.3.6 mTOR targeted therapy in RCC

Temsirolimus

The mTOR inhibitor temsirolimus was approved for treatment of advanced RCC in May of 2007. Its efficacy and safety were demonstrated in the pivotal phase 3 ARCC trial, a global, randomized, open-label study in 626 previously untreated patients with advanced RCC who had 3 or more of 6 poor prognostic factors (Hudes, Carducci et al. 2007). Patients were randomized to temsirolimus, interferon or both. Single-agent temsirolimus was associated with a statistically significant improvement in overall survival (OS) when compared to IFN (hazard ratio 0.73 [95% CI: 0.58, 0.92]; p= 0.0078). The median OS was 10.9 months on the temsirolimus arm and 7.3 months on the IFN arm. Median PFS was 5.5 months on the temsirolimus arm and 3.1 months on the IFN arm [hazard ratio 0.66 (95% CI: 0.53, 0.81)] in this poor risk population. The combination of 15 mg temsirolimus and IFN did not result in a significant increase in OS when compared with IFN alone and was associated with an increase in multiple adverse reactions.

Unlike all other phase 3 trials of targeted agents in RCC, this study included both patients with conventional and non-clear cell histologies. Patients with histologies other than clear cell RCC accounted for 17% and 18% in the temsirolimus and interferon group, respectively. This included patients of non-clear cell and indeterminate histology. Subgroup analysis for this patient subset suggests superior median OS and PFS for temsirolimus vs IFN with HR of 0.49 (95% CI = 0.29,0.85) and 0.38 (95% CI = 0.23,0.62), respectively (Dutcher, de Souza et al. 2009). While median OS was shorter in NCRCC compared to conventional RCC, efficacy of temsirolimus appeared more pronounced among patients with non-clear or indeterminate primary cell type than among those with clear cell histology. This might be due to the fact that IFN has less efficacy in the former group of patients as mentioned above (Motzer, Bacik et al. 2002).

Everolimus

Everolimus is an oral derivative of rapamycin. It 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. It has been in development for patients with various malignancies since 2002. Everolimus has been 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.

Everolimus has been evaluated as a single agent and in combination with other antitumor agents, including cytotoxic chemotherapeutic agents, targeted therapies, antibodies and hormonal agents. Phase I dose escalating studies, exploratory Phase I/II studies with everolimus as single agent or in combination with other anti-cancer agents, Phase II/III studies of everolimus in several indications, and Phase III double-blind studies are contributing to the extensive database.

Everolimus was recently approved under the trade name Afinitor® for patients with advanced RCC after failure of treatment with Sutent® (sunitinib) or Nexavar® (sorafenib) in the US, EU and several other countries and is undergoing registration in other regions worldwide. FDA approval was based on a pivotal phase 3 trial, an international, multicenter, randomized, double-blind study comparing everolimus to placebo in 410 patients pretreated with sunitinib or sorafenib (Motzer, Escudier et al. 2008). Prior therapy with bevacizumab, interleukin-2, or interferon-α was also permitted. Everolimus showed superior PFS over placebo (4.0 mo vs 1.9 mo, HR 0.3, CI 0.22-0.40, $p<0.0001$). ORR was 1% for everolimus, none for placebo, arguing that PFS benefit is likely due to disease stabilization. This trial extended the role of mTOR inhibitors beyond first line therapy, and everolimus is now considered the standard of

care in patients with metastatic conventional RCC, whose disease has progressed after treatment with VEGF-targeted therapies.

The most common adverse reactions (incidence ≥10%) were stomatitis, rash, fatigue, asthenia, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, pneumonitis, cough, peripheral edema, infections, dry skin, epistaxis, pruritus, and dyspnea. The most common grade 3-4 adverse reactions (incidence ≥2%) were infections, stomatitis, fatigue, and pneumonitis. Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Everolimus and some of these cases have been severe and on rare occasions, fatal outcomes have been observed. Deaths due to acute respiratory failure (0.7%), infection (0.7%), and acute renal failure (0.4%) were observed on the everolimus arm. The rates of treatment-emergent adverse reactions resulting in permanent discontinuation were 7% and 0% for the everolimus and placebo treatment groups, respectively.

The most common laboratory abnormalities (incidence ≥50%) were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine. The most common grade 3/4 laboratory abnormalities (incidence ≥3%) were lymphopenia, hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia.

Overall, safety data available from completed, controlled and uncontrolled studies are consistent with the aforementioned findings of the Phase III trial. Everolimus is generally well tolerated at weekly and daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative. Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to respiratory or hepatic failure) and occasionally have had a fatal outcome.

3.3.7 Everolimus Pharmacokinetics / Pharmacodynamics

Everolimus is rapidly absorbed with a median tmax of 1-2 hours. The steady-state AUC0-τ is dose-proportional over the dose range between 5 and 10 mg with daily administration, steady-state was achieved within two weeks with the daily dosing regimen. Cmax is dose-proportional between 5 and 10 mg daily administration. In healthy subjects, high fat meals reduced systemic exposure to everolimus 10 mg (as measured by AUC) by 22% and the peak plasma concentration Cmax by 54%. Light fat meals reduced AUC by 32% and Cmax by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Following oral administration, everolimus is the main circulating component in human blood and is considered to contribute the majority of the overall pharmacologic activity. No specific excretion studies have been undertaken in cancer patients; however, data available from the transplantation setting found the drug to be mainly eliminated through the feces. The mean elimination half-life of everolimus is approximately 30 hours.

Everolimus is a substrate of CYP3A4 and a substrate and moderate inhibitor of PgP. Please refer to Section 9.5.1 for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

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 (Kulke, Lenz et al. ; Maki, Fletcher et al.).

3.3.8 Tissue biomarkers for mTOR targeted therapy in RCC

Investigating the prognostic significance of mTOR pathway components in RCC, a study of 375 pts with resected disease (including 14% non clear-cell RCCs) observed adverse prognostic impact of pS6K, PTEN and Akt on disease-specific survival, independent of stage (Pantuck, Seligson et al. 2007). A second smaller study further suggested that pS6K and possibly pAkt were predictors of response to temsirolimus for advanced RCC (Cho, Signoretti et al. 2007).

3.3.9 Combining different targeted agents in RCC

The approach of combining active agents with different mechanisms of action has proven valuable in the development of cytotoxic chemotherapy regimens in other cancers, and is subject of extensive investigation in targeted agents. Such treatment aims to improve responses, and either prevent or circumvent development of resistance. In phase I clinical trials, however, tolerability varies. Some combinations have required dose reductions (e.g. sunitinib with everolimus (Kroog, Feldman et al. 2009)), others are not considered safe to be given together (sunitinib with temsirolimus (Fischer, Patel et al. 2008)).

In a phase I trial of 26 patients with conventional RCC, the combination of sunitinib with bevacizumab yielded ORR of 52% with the maximum tolerated dose (MTD) determined at full doses for both agents, but on further follow-up there was a high degree of treatment-associated hypertension, vascular and hematologic toxicities at these dose levels (Feldman, Baum et al. 2009).

In NCRCC mutations in the VHL gene are not commonly seen, yet elevations in VEGF and HIF levels are thought to occur in response to the hypoxic tumor environment. Despite normal *VHL* function, some non-clear cell RCC have been found to exhibit a highly activated mTOR pathway (Pantuck, Seligson et al. 2007). Importantly, mTOR downstream effectors eIF-4E and phospho-S6 increase levels of both VEGF and HIF-1α(Azim, Azim et al. 2010). HIF-1α induces further increase in VEGF levels. VEGF, in turn, through its receptor, activates the PI3-K/Akt/mTOR axis(Agarwala and Case 2010). Inhibition of several steps in this autocrine loop (mTOR–HIF–VEGF-mTOR) is thought to be superior to single agents used in sequence(Heng and Choueiri 2009), and preclinical models have found such combinations to be synergistic(Ikezoe, Nishioka et al. 2006; Ikezoe, Yang et al. 2006). Our group previously conducted a phase I study combining VEGF and mTOR-inhibition by use of sunitinib and everolimus in 20 treatment-naïve patients with advanced RCC, 13 with clear cell and 7 with

non-clear cell histology(Kroog, Feldman et al. 2009). 5/20 patients (25%) achieved a partial response (PR), ten patients (50%) had stable disease. Three of the five patients with PR had non-clear cell histology, accounting for a RR of 43% within this subgroup; all three remained on protocol for more than one year, arguing in favor of combined targeting of VEGF and mTOR in these patients. Unfortunately, the combination was only tolerated at attenuated doses, and significant toxicity was observed. Treatment was associated with diverse grade 3/4 toxicities, and the combination is not recommended for further study.

3.3.10 Combination of Everolimus and Bevacizumab

Preclinical studies of Everolimus plus VEGF Inhibition

Everolimus has been studied in combination with a VEGFR tyrosine kinase inhibitor called PTK787/ZK222584 (vatalanib) in tumor models. Comparisons of the effects of everolimus with those of PTK787/ZK222584, on angiogenic processes in vitro and in vivo, indicated overlapping effects on endothelial cell proliferation consistent with an integral role of the mTOR pathway in VEGFR signaling. Based on this data, there is a potential for synergy between everolimus and VEGF inhibitors, such as PTK787/Zk222584 and bevacizumab.

Clinical experience with Everolimus plus Bevacizumab

Phase 1 and 2 studies have investigated the combination of everolimus and bevacizumab. Full dose of bevacizumab 10 mg/kg, i.v. every 2 weeks and full dose of everolimus 10 mg, p.o. daily given together has shown to be tolerable.

A Phase 1 dose-escalation study of bevacizumab, everolimus, and erlotinib in patients with advanced-stage solid tumor demonstrated that the combination of everolimus and bevacizumab was well tolerated, allowing full doses of both agents to be administered. The study included four dose levels:

	Bevacizumab	Everolimus	Erlotinib
Dose Level 1	10 mg/kg every 2 wks	5 mg daily	---
Dose Level 2	10 mg/kg every 2 wks	10 mg daily	---
Dose Level 3	10 mg/kg every 2 wks	10 mg daily	75 mg daily
Dose Level 4	5 mg/kg every 2 wks	5 mg daily	75 mg daily

Fifteen patients were treated in Dose Level 2 (bevacizumab 10 mg/kg every 2 weeks and everolimus 10 mg daily), and no dose-limiting toxicities were seen in this dose level (Bendell, Gerorge et al. 2007). A total of 20 patients received bevacizumab and everolimus. The most common adverse events were mild or moderate mucositis, fatigue, rash, and musculoskeletal pain. In the group of patients who received everolimus and bevacizumab (20), there were six Grade 3 events, one of each of the following: proteinuria, deep vein

thrombosis, cardiac ischemia, liver enzyme elevation, partial bowel obstruction, and rash. There were three Grade 4 events, one of each of the following: proteinuria, left ventricular thrombus, and left ventricular systolic dysfunction (Bendell, Gerorge et al. 2007).

A recent single arm phase II trial evaluated the efficacy of everolimus in combination with bevacizumab in 80 subjects with advanced RCC, including both untreated (Group A, 50 pts) and pretreated patients (Group B, 30 pts) (Hainsworth, Spigel et al. 2010). Enrollment required clear cell RCC, for mixed-histology tumors, the clear cell component had to comprise more than 75% of the biopsy specimen. Patients received bevacizumab 10mg/kg intravenously every 2 weeks and everolimus 10mg orally daily. Patients were evaluated for response after 8 weeks of treatment and continued treatment until disease progression or unacceptable toxicity. Median age was 63 (group A) and 64 (group B), the majority of patients had low or intermediate MSKCC risk scores. Among the 30 patients in group B, 16 had previously received sunitinib treatment, 12 sorafenib treatment, 2 immunotherapy. ORR was 30% and 23% in un- and pretreated patients, respectively. The median PFS and OS were 9.1 months and 21.3 months for group A, 7.1 months and 14.5 months for group B.

Table-3.2 Efficacy of Everolimus/Bevacizumab in conventional RCC, phase II data by Hainsworth et al.(Hainsworth, Spigel et al. 2010)

	Group A (N=50)	Group B (N=30)
Complete response	1 (2%)	1 (3%)
Partial response	14 (28%)	6 (20%)
Stable	25 (50%)	19 (64%)
Progression	3 (6%)	3 (10%)
Unevaluable	7 (14%)	1 (3%)
Median PFS	9.1 months	7.1 months
Median OS	21.3 months	14.5 months

The combination was well tolerated by most patients, although grade 1 to 2 toxicities were relatively common. Adverse effects observed were those expected, based on the individual toxicity profiles of these two agents. The most common grade 3 to 4 toxicities included proteinuria (26%), mucositis/stomatitis (15%), fatigue (12%), and diarrhea (9%). The most common grade 3 to 4 toxicities included proteinuria (26%), mucositis/stomatitis (15%), fatigue (12%), and diarrhea (9%). The incidence of grade 3 to 4 proteinuria of 26% was higher than reported with single-agent bevacizumab, raising the possibility of potentiation of this toxicity by the combination; in most patients, grade 3 proteinuria was rapidly reversible when treatment with bevacizumab was interrupted, those patients were able to resume treatment at a later point. Twenty-five additional patients had dose adjustments of everolimus at some time during therapy, but were able to continue treatment with the modified dose regimen.

Based preliminary findings from this trial, two large studies were designed, which are ongoing, one a first-line, large randomized phase II study comparing this regimen to the combination of bevacizumab and interferon (RECORD 2), and one second-line phase III post sunitinib study, comparing the same regime to everolimus plus placebo (proposed by the Cancer and Leukemia Group B).

3.4 Rationale for this study

There is no current standard of care for the treatment of patients with metastatic NCRCC, and phase 2 trials of single agent VEGF targeted TKI in this group have been disappointing (Ravaud, Oudard et al. 2009; Molina, Feldman et al. 2010; Plimack, Jonasch et al. 2010). As outlined above, unplanned secondary analyses from two large phase III trials that have helped establish temsirolimus and bevacizumab in the treatment of conventional RCC suggest efficacy to both mTOR and VEGF pathway inhibition in NCRCC (Escudier, Ravaud et al. 2008; Dutcher, de Souza et al. 2009), however the numbers are too small to draw definite conclusions. There is a molecular rationale for combining agents targeting both pathways in NCRCC, since inhibition of several steps in an autocrine loop (mTOR–HIF–VEGF-mTOR) is thought to be superior to single agents used in sequence (Heng and Choueiri 2009). We chose everolimus over temsirolimus for two reasons: for one, since it is easily self-administered at home, whereas temsirolimus requires weekly visits for intravenous infusion of drug; secondly, since everolimus has been studied and found to be well tolerated in combination with bevacizumab in both the phase I and II setting, even with both drugs given at full doses. The purpose of this single-arm, single-center Phase II study is to determine the efficacy and safety of everolimus 10 mg p.o. daily dose in combination with bevacizumab 10 mg/kg administered intravenously every two weeks for treatment of patients with advanced non-clear cell carcinoma of the kidney, who have not received prior mTOR- or VEGF-targeted treatments.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single-institution, single-arm phase II trial of everolimus in combination with bevacizumab in patients with advanced non-clear cell RCC, who have not received prior VEGF-.or mTOR-targeted therapy. This study is designed as a single-stage trial which requires a total of 34 patients. If 22 or more patients are progression-free after 6 months from the first day of treatment, this regimen will be considered feasible and will merit further clinical study.

A separate cohort of patients with non-clear cell RCC with papillary features will be enrolled in order to gather information regarding the efficacy given the rarity of these entities.

4.3 Intervention

Cycle length will be defined as 28 days. Treatment will include everolimus 10mg, self-administered orally once daily on a continuous schedule (days 1-28), and bevacizumab 10mg/kg, administered intravenously on days 1 and 15 of each cycle.

Treatment will be continued until disease progression, major toxicity, or withdrawal from the study for any reason. Dose modification will be permitted based on toxicity as described in section 9.0.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Everolimus

Everolimus is formulated as tablets of 2.5 mg, 5 mg, and 10 mg strength, blistered 28 tablets per box.. Tablets should be kept in the blister packs until the time of administration as the drug is both hygroscopic and light-sensitive. Everolimus will be supplied through Novartis.

5.2 Bevacizumab

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile pH6.2 solution for intravenous infusion. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 8 hours in the refrigerator at 36°F to 46°F (2°C to 8°C), unless dilution has taken place in controlled and validated aseptic conditions. Bevacizumab should not be frozen. Keep the vial in the outer carton in order to protect from light.

Bevacizumab does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Bevacizumab will be prepared and administered as per MSKC guidelines.

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags or infusion sets have been observed. Bevacizumab infusions should not be administered or mixed with glucose solutions.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Advanced renal cell carcinoma of non-clear cell histology with papillary features, histologically confirmed by MSKCC pathology. Advanced disease is defined as unresectable, locally recurrent disease or metastatic disease. Availability of additional tissue for correlative studies is NOT in inclusion requirement.
2. Evidence of unidimensionally measurable disease per RECIST 1.1 (Eisenhauer, Therasse et al. 2009).
3. Resolution of all acute toxic effects of prior radiotherapy or surgical procedures to NCI CTCAE Version 4.0 grade ≤1.
4. Adequate organ function as defined by the following criteria:
    - Absolute neutrophil count (ANC) ≥1,500/μL
    - Platelets ≥100,000/μL
    - Hemoglobin ≥9.0 g/dL
    - Serum calcium ≤12.0 mg/dL
    - Serum creatinine ≤1.5 x ULN
    - Total serum bilirubin ≤ 2.0 x ULN
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase

[SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤2.5 x local laboratory upper limit of normal (ULN), or AST and ALT ≤5 x ULN if liver function abnormalities are due to underlying malignancy

- INR ≤1.5. (Anticoagulation is allowed if target INR ≤ 1.5 on a stable dose for >2 weeks at time of study entry.)
- Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

5. Karnofsky performance status ≥ 70 %.
6. 18 years of age or older.
7. Ability to swallow oral medication.
8. Signed and dated informed consent document indicating that the subject (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to undergoing study screening procedures.
9. Subject‟s willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

6.3 Subject Exclusion Criteria

1. Patients who have received prior systemic therapy for their RCC with VEGF pathway inhibitor (such as sunitinib, sorafenib, and bevacizumab) or with mTOR inhibitors (such as sirolimus, temsirolimus, everolimus, or deforolimus).
2. Patients within 28 days post major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic), open biopsy, or significant traumatic injury to avoid wound healing complications. Minor procedures and percutaneous biopsies or placement of vascular access device without complications require 48 hours prior to study entry.
3. Patients who had radiation therapy within 28 days prior to start of study treatment (palliative radiotherapy to bone lesions allowed if completed 2 weeks prior to study treatment start).
4. Patients with evidence or history of central nervous system (CNS) metastases or spinal cord compression, unless prior treatment with surgery or radiotherapy AND no progression of CNS disease within 6 months prior to enrollment.
5. Patients with a history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to study enrollment.
6. Patients with proteinuria on screening urinalysis confirmed to be >1g /24h by 24 hour urine collection.
7. Patients with inadequately controlled hypertension (defined as a blood pressure of > 150 mmHg systolic and/or > 100 mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy.
8. Patients receiving chronic systemic treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisone equivalent) or another immunosuppressive agent. Inhaled and topical steroids are acceptable.
9. Patients with a known history of HIV seropositivity.
10. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:

- unstable angina pectoris (at any time), symptomatic congestive heart failure (NYHA III, IV) (at any time), serious uncontrolled cardiac arrhythmia (at any time), myocardial infarction, cerebrovascular accidents, or symptomatic left ventricular dysfunction ≤ 6 months prior to first study treatment.
- active bleeding diathesis
- known severely impaired lung function defined as spirometry and DLCO ≤ 50% of normal and oxygen saturation at rest ≤ 88% on room air
- symptomatic intrinsic lung disease requiring oxygen supplementation at baseline
- Uncontrolled diabetes mellitus as defined by HbA1c >8% despite adequate therapy. Patients with a known history of impaired fasting glucose or diabetes mellitus (DM) may be included, however blood glucose and antidiabetic treatment must be monitored closely throughout the trial and adjusted as necessary
- any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study
- liver disease such as cirrhosis, decompensated liver disease, or active and chronic hepatitis (i.e. quantifiable HBV-DNA and/or positive HBsAg, quantifiable HCV-RNA)

11. Patients who have a history of another primary malignancy and are off treatment for ≤ 3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of the uterine cervix.
12. Female patients who are pregnant or breast feeding
13. Women of child-bearing potential (WOCBP), defined as all women physiologically capable of becoming pregnant, must use highly effective methods of contraception during the study and 8 weeks after. Highly effective contraception methods include combination of any two of the following:
    a. Use of oral, injected or implanted hormonal methods of contraception or;
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS);
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository;
    d. Total abstinence or;
    e. Male/female sterilization

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

14. Male patients whose sexual partner(s) are WOCBP who are not willing to use adequate contraception, during the study and for 8 weeks after the end of treatment.
15. Patients who are using other investigational agents or who had received investigational drugs ≤ 4 weeks prior to study treatment start.
16. Patients who have received attenuated live vaccines within one week of study entry. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

17. Known intolerance or hypersensitivity to Everolimus or other rapamycin analogs (e.g. sirolimus, temsirolimus).
18. Known impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Everolimus.
19. Patients with a history of non-compliance to medical regimens or who are considered potentially unreliable or will not be able to complete the entire study

7.0 RECRUITMENT PLAN

Patients will be recruited through the outpatient clinics of the Solid Tumor Division of MSKCC. Both men and women and members of all ethnic groups are eligible for this trial.

Potential research subjects will be identified by a member of the patient"s treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient"s medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

8.1 PRETREATMENT EVALUATION

Prior to undergoing any study-specific procedure, subjects must read and sign the current Institutional Review Board (IRB)-approved informed consent form.

Screening Procedures Within 28 Days:

- Subject signature on current IRB-approved informed consent form
- Tumor imaging including CT scan of the chest, abdomen, and pelvis and other applicable sites of disease. Patients who cannot receive intravenous (IV) contrast will undergo imaging with CT chest without IV contrast and MRI of the abdomen/pelvis.
- Brain CT or MRI with contrast, if clinically indicated
- Bone scan, if clinically indicated
- Pulmonary Function Tests to include spirometry, DLCO and oxygen saturation at rest, if clinically indicated

Screening Procedures within 14 Days Prior to Starting Treatment:

- Medical history including oncologic history, history of other disease processes (active or resolved), concomitant illnesses and demographics
- Karnofsky performance status, body weight, height, and vital signs (temperature, blood pressure, heart rate, respiratory rate)
- Assessment of concomitant medications and treatments
- Physical examination including examination of major body systems and
- Hematology: CBC, differential, platelets

- Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, LDH, sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, and fasting glucose (patients must be fasting x 6h)
- Baseline lipid panel (patients must be fasting x 6h)
- PT/INR
- HbA1c, only for patients with a history of diabetes mellitus (DM)
- Urinalysis; (reflexive 24h urine collection for protein quantification to be obtained, if any degree of proteinuria seen on urinalysis [see also section 6.2])
- Serum pregnancy test, if applicable
- 12-lead ECG
- Screening for hepatitis B. Per MSKCC standard policy for any patient receiving anti-cancer therapy, HB Surface Antigen and HB core Antibody will be tested with HBV PCR performed reflexively for any abnormal results (see appendix)
- Screening for Hepatitis C. HCV RNA-PCR and Hepatitis C Antibody will be tested for all patients at screening.

Correlative Studies:

- Unstained slides will be obtained for each patient enrolled in the initial cohort only. Availability of such tissue specimen is not a requirement for study participation, and receipt of the material is not mandatory for initiation of treatment, i.e. can be obtained thereafter.

9.1 TREATMENT/INTERVENTION PLAN

Cycle length is defined as 28 days. Treatment will include everolimus 10mg, self-administered orally once daily on a continuous schedule (days 1-28), and bevacizumab 10mg/kg, administered intravenously on days 1 and 15 of each cycle.

9.2 Everolimus Dosing Instructions

Patients will take the first dose of everolimus at the center on Cycle 1, Day 1. Thereafter, patients will be instructed to swallow everolimus orally with a glass of water immediately after a meal, once daily at the same time each day. Any dietary habits around the time of everolimus intake should be as consistent as possible throughout the study. The tablet(s) should not be chewed or crushed. If vomiting occurs, no attempt should be made to replace the vomited dose unless the everolimus tablet(s) are clearly visible. If the tablet(s) are clearly visible, then the patient should replace the everolimus dose.

If a dose of everolimus is missed, patients will not increase the following day"s dose. Instead, treatment will continue on the same schedule with no change in dosage or timing of drug administration. Missed doses should be documented by the patient in the pill diary in order to inform the treating physician at the next clinic visit.

Patients will continue to take everolimus until disease progression, major toxicity, or withdrawal from the study for any reason.

The maximum allowed time of interruption of everolimus is 3 weeks in general, and up to 4 weeks in the setting of Hepatitis B reactivation.

In the event of permanent discontinuation of bevacizumab for safety reasons, everolimus may continue in the absence of disease progression. Patients continuing on everolimus only are only required to come for Day 1 visits each cycle. Other visits are not required.

9.3 Bevacizumab Administration

Patients will receive an intravenous infusion of bevacizumab 10 mg/kg on Cycle 1, Day 1 and will return to the center every two weeks (14 days) for subsequent infusions until disease progression, major toxicity, or withdrawal from the study for any reason.

The maximum allowed time of bevacizumab interruption is 8 weeks.

In the event of permanent discontinuation of everolimus for safety reasons, bevacizumab may continue in the absence of disease progression.

9.4 Dose Modifications

Dose reductions will be performed, depending on the type and severity of the toxicity encountered, provided that the criteria have not been met for subject withdrawal from study. Recovery to acceptable levels of toxicity, as defined in the tables below, must occur within 4 weeks to allow continuation in the study.

9.4.1 Everolimus Dose Modifications

9.4.1.1 Dose Modifications for Hepatic Impairment

Patients with decompensated hepatic function or cirrhosis at baseline are not permitted to enter this study. See also section 6.1 for enrollment requirements of serum liver function tests.

For dose adjustments in the setting of hepatic toxicity on study therapy, refer to section 9.3.1.3. Note that in the setting of multiple factors indicating hepatic dysfunction, even if mild / low grade, patients with Child-Pugh class B hepatic dysfunction (see appendix) should be dose reduced to 5mg daily per everolimus labeling (see appendix).

9.4.1.2 Dose Modifications for Renal Impairment

No dose modifications are recommended.

9.4.1.3 Dose Modification due to Toxicity

If treatment is interrupted due to toxicity, everolimus should not be resumed until recovery to ≤ Grade 1, then reintroduce everolimus at the initial dose or lower dose level depending on toxicity type and Grade (Table 9.2). Both drugs (everolimus and bevacizumab) are to be held until the guidelines outlined below deem that both are safe to be restarted. These changes

must be recorded. For additional instructions on management including dose modifications in the setting specific toxicities, see section 11.2.

Table 9.1 Dose reduction steps for everolimus

Dose Level	Dose and Schedule
0 (starting dose)	10 mg, p.o. daily
Decrease 1 dose level	5 mg, p.o. daily
Decrease 2 dose level	5 mg, p.o. every other day

If a patient has already decreased 2 dose levels, no further dose reduction is permitted. Patients requiring a third dose reduction must discontinue everolimus. The maximum allowed time of interruption of everolimus is 3 weeks in general and up to 4 weeks in case of Hepatitis B reactivation.

Table 9.2 Suspected Everolimus Toxicity – Dose Modification and Reinitiation

Toxicity	**Action**
Non-hematological toxicity	
Grade 2 (except pneumonitis - refer to table 11.1)	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 ≤ Grade1. Then reintroduce everolimus at the lower dose level. Suspend Bevacizumab dosing while everolimus is being held.
Grade 3	Interrupt everolimus and Bevacizumab until recovery to ≤ Grade 1. Then reintroduce Bevacizumab at starting dose and everolimus at the lower dose level. 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 everolimus until recovery to ≤ Grade 1 (>75 x10^9/L). Then reintroduce everolimus at initial dose. Suspend Bevacizumab dosing while everolimus is being held. If thrombocytopenia again returns to Grade 2, interrupt everolimus and bevacizumab until recovery to ≤ Grade 1. Then reintroduce everolimus at the lower dose level and resume bevacizumab at starting dose.
Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt everolimus and Bevacizumab until recovery to ≤ Grade 1 (platelets ≥ 75 x10^9/L). Then reintroduce Bevacizumab at starting dose and resume everolimus at one dose level lower. If Grade 3 thrombocytopenia recurs, discontinue everolimus.
Grade 4 Thrombocytopenia (platelets < 25 x10^9/L)	Discontinue everolimus.
Grade 3 Neutropenia (neutrophils <1, ≥0.5	Interrupt everolimus and Bevacizumab until recovery to ≤

Toxicity	Action
x10^9/L)	Grade 1 (neutrophil ≥ 1.5 x 10^9/L). Then reintroduce Bevacizumab at starting dose and resume everolimus at the initial dose. If ANC again returns to Grade 3, hold everolimus and Bevacizumab until the ANC ≥ 1.5 x 10^9/L. Then reintroduce Bevacizumab at the starting dose and resume everolimus dosing at the lower dose level. Discontinue patient from study therapy for a third episode of Grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt everolimus and Bevacizumab until recovery to ≤ Grade 1 (neutrophil ≥ 1.5 x 10^9/L). Then reintroduce Bevacizumab at starting dose and resume everolimus at the lower dose level. If ≥ Grade 3 neutropenia occurs despite this dose reduction, discontinue everolimus.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt everolimus and Bevacizumab until resolution of fever and neutropenia to ≤ Grade 1. Hold further everolimus and Bevacizumab until the ANC ≥ 1,500/mm^3 and fever has resolved. Then reintroduce Bevacizumab at starting dose and resume everolimus at the lower dose level. If febrile neutropenia recurs, discontinue everolimus.
Grade 4 febrile neutropenia (life-threatening)	Discontinue everolimus.
Any hematological or non-hematological toxicity requiring interruption for > 3 weeks except in the case of hepatitis B reactivation which is > 4 weeks	Discontinue everolimus.

9.4.1.4 Dose Modifications related to CYP3A4 / P-glycoprotein (PgP)

Everolimus is metabolized primarily by liver enzymes, in particular CYP3A4. It is also a moderate inhibitor of the multidrug efflux pump PGP. Drugs or substances known to be inhibitors, inducers or substrates of the isoenzyme CYP3A4 or PgP should be avoided unless use of the drug is essential and no substitute is available. See tables 9.3 and 9.4 for a listing of relevant medications with effects on everolimus metabolism through CYP3A4 and/or PgP.

- **Inhibitors of CYP3A4 and/or PgP**

Co-administration with moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided. Patients, who are taking such medications prior to enrollment, should be switched to an alternate agent without effect on CYP3A4 / PgP prior to or at the time of study initiation, if possible.

If a patient requires co-administration of moderate / strong CYP3A4 or PgP inhibitor which cannot be discontinued or replaced, the subject will start everolimus at the standard dose (10mg by mouth daily). In the event that toxicity occurs, everolimus interruptions and dose modifications should be undertaken as outlined in section 9.3.1.3. For such patients, who undergo dose reductions, everolimus can be re-escalated to the previous dose, once the CYP3A4/PgP inhibitor is discontinued for whichever reason.

Seville orange, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.

- **Inducers of CYP3A4 and/or PgP**

Concomitant use of strong CYP3A4 inducers during study treatment should be avoided, if possible. Patients, who are taking such medications prior to enrollment, should be switched to an alternate agent without effect on CYP3A4 / PgP prior to or at the time of study initiation, if possible.

If a patient requires co-administration of moderate / strong CYP3A4 or PgP inhibitor which cannot be discontinued or replaced, then the subject will start everolimus at the standard dose (10mg by mouth daily) with the aim to subsequently increase everolimus by 50%. Enzyme induction usually occurs within 7-10 days; therefore everolimus dose should not be escalated during this time. Instead, the dose will be increased to 15mg daily after at least 14 days of concomitant therapy has been administered without safety concerns up to that point. No additional dose-escalations will be made. In case everolimus has been escalated to 15mg daily and the patient experiences toxicity that would require a dose reduction per table 9.2, everolimus will be dose-reduced to 10mg daily. Subsequent dose modifications should follow the guidelines lined out in section 9.3.1.3.

If the strong inducer is discontinued in a patient previously dose-increased to everolimus 15mg daily, the everolimus dose should be de-escalated to everolimus 10mg daily.

- **HMG-CoA reductase inhibitors and CYP3A4**

Studies in healthy subjects indicate that there are no clinically significant pharmacokinetic interactions between everolimus and the HMG-CoA reductase inhibitors atorvastatin (a CYP3A4 substrate) and pravastatin (a non-CYP3A4 substrate). A population pharmacokinetic analysis also detected no influence of simvastatin (a CYP3A4 substrate) on the clearance of everolimus (taken from everolimus package insert, see appendix)

Table 9.3 Clinically relevant drug interactions: substrates / inducers / inhibitors of CYP3A4

INDUCERS
Barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate
INHIBITORS
Strong inhibitors: **clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole,** **Posaconazole (Krishna et al, 2009)** Moderate inhibitors: **aprepitant, atazanavir, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice, imatinib, tofisopam, verapamil,**

Table 9.4 List of clinically relevant drug interactions mediated by PgP

PgP substrates	PgP inhibitors in vivo	PgP inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	**amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole, ketocoanzole, lopinavir,**	**rifampin, St John's wort**

PgP substrates	PgP inhibitors in vivo	PgP inducers
	(LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	

Reference:

Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Dec. 2, 2009, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table. "

This list of clinically relevant drug interactions is updated as of December 02, 2009

9.3.2 Bevacizumab Dose Modifications

There are no recommended dose modifications for the use of bevacizumab, other than dose adjustments due to change(s) in body weight (patient"s body weight changes by ± 10% from baseline). Body weight at baseline will be used to calculate the required dose. Once an adjustment has been made, the adjusted dose will become the new reference for potential further dose changes.

If needed, bevacizumab should be either discontinued or temporarily suspended as described below. Hold bevacizumab whenever adverse events require temporary suspension of everolimus. Bevacizumab can be restarted at the original dose, once the protocol requirements for re-initiating everolimus are met. The maximum allowed time of bevacizumab interruption is 8 weeks.

Appropriate diagnostic and therapeutic medical treatment including accurate hypertensive treatment is mandatory for patients developing signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS). Bevacizumab has to be discontinued in these patients. The safety of re-initiating bevacizumab in patients previously experiencing RPLS is not known.

Bevacizumab should be permanently discontinued for the following toxicities:

- gastrointestinal perforation
- arterial thromboembolic event
- Grade 3/4 hemorrhagic event
- Wound dehiscence and wound healing complications requiring medical intervention
- symptomatic Grade 4 thrombosis
- Grade 4 hypertension or hypertensive encephalopathy
- nephrotic syndrome

For additional instructions on the management of specific toxicities, please see section 11.7.

9.3.2.1 Bevacizumab and drug interactions

No formal drug interaction studies with other agents have been conducted for bevacizumab.

9.4 Compliance

Subjects will be required to keep a pill diary documenting daily self-administration of everolimus at home. Bottles of study medication must be returned at the beginning of each new cycle. The number of tablets remaining will be documented and recorded. Subjects who are considered non-compliant will be withdrawn from study.

Patients who receive less than 50% of the recommended everolimus dose during a treatment cycle for reasons other than toxicity will be documented as protocol deviations and will be reviewed by the study PI to determine if they should be discontinued from the study.

9.5 Concomitant Medication(s)

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with/approval from the investigator. All medications taken within 30 days of starting study treatment must be reviewed as per the recommendations below.

Patients will be instructed to notify the study center about any new medications he/she takes after the start of the study treatment.

Investigational or commercial anticancer agents other than everolimus plus bevacizumab are not allowed during the study. The initiation of any non-protocol specific anti-tumor treatment or surgery is considered an indication of disease progression and should be recorded appropriately.

9.5.1 Anticoagulative agents

Anticoagulation is allowed if target INR is ≤ 1.5 on a stable dose for >2 weeks. Similarly, in patients who experience thromboembolic events during study treatment, initiation of full dose anticoagulants is permitted.

9.5.2 Palliative radiotherapy or initiation of bisphosphonates

Bisphosphonate therapy for the treatment of bone lesions may be initiated before the patient enters the study.

Patients who require palliative radiotherapy during treatment should be evaluated carefully for possible disease progression. Localized radiotherapy, for the treatment of pre-existing, painful bone metastases is allowed during the study only if evidence of radiological progression is not present. Palliative radiotherapy to bone is allowed to treat for pain, not for disease progression. Previously irradiated bone lesions will be evaluable for disease progression and stable disease only. If palliative radiotherapy is prescribed, interrupt everolimus for the duration of the radiation treatment. If everolimus interruption is greater than 21 days, the patient must be permanently discontinued with exception of Hepatitis B reactivation, where a maximum of 4 weeks treatment interruption is acceptable.

Radiotherapy for brain metastases is not permitted during the course of the study; because the need for CNS radiation will constitute disease progression.

Pain medication is allowed for the patient to be as comfortable as possible.

9.5.3 Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with everolimus. These include, but are not limited to: intranasal influenza, measles, mumps, rubella, varicella, oral polio, BCG, yellow fever, and TY21a typhoid vaccines.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

10.1 Evaluation performed with scheduled follow-up at each cycle

The following procedures must be performed on the days indicated for each / every other cycle:

- Karnofsky performance status and Physical Examination including major body systems (Day 1 ± 5 days*; Day 15 ± 5 days only on cycle 1*)
- Vital signs and weight (Day 1, 15 ± 5 days)
- Assessment of adverse events and tumor-related signs and symptoms (Day 1 ± 5 days; *Day 15 ± 5 days only on cycle 1*)
- Assessment of concomitant medications and treatments (Day 1 ± 5 days)
- Hematology: Complete blood cell count (Days 1, 15 ± 5 days)
- Blood Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, LDH, sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose (Days 1 ± 5 days)
- Fasting glucose once every 2 cycles [patients must be fasting x 6h] (Day 1 ± 5 days)
- Lipid Panel once every 2 cycles [patients must be fasting x 6h] (Day 1 ± 5 days)
- Urine chemistry once every 2 cycles: Urinalysis with dipstick will be performed for detection of proteinuria with reflective quantification of random protein and creatinine to calculate urine protein-creatinine ratio (UPCR) per section 11.2.10 (Day 1 ± 5 days)
- Pre-treatment blood sample for correlative studies (Cycle 1, Day 1 only) Not applicable for patients enrolled in the expansion cohort.
- Dispense everolimus to subject (Day 1 ± 5 days)
- Administration of bevacizumab (Days 1, 15 ± 5 days)

Table 10.1 Study Treatment Schedule

		Cycle 1				Cycle 2				Cycle 3+[j]				
	Pre-Study[a]	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12+	Off Study[b]
Bevacizum ab		X		X		X		X		X		X		

Everolimus	Taken orally every morning													
Tumor for pS6, pAKT, HIF-1α, PTEN[i]	X													
Research Test: blood sample[e]		X												
Informed consent	X													
Doctor"s visit	X	X		X		X				X				X
Blood tests[c]	X	X		X		X		X		X		X		X
Fasting blood draw (glucose and lipids)	X	X								X				X
Urine tests	X	X								X				X
EKG	X													
CT or MRI scans of chest, abdomen and pelvis[d]	X	Every 8weeks[d]												X
Pulmonary Function Tests (PFTs)	X[f]													
Pregnancy test	X[g]	X[h]				X[h]				X[h]				

a: within 28 days before first dose of treatment
b: within 28 days after last dose of treatment
c: you must be fasting, i.e. no calory intake for 6 hours prior to this blood-draw
d: after 6 cycles (24 weeks), scans will be every 12 weeks.
e: The blood sample for correlative studies will be taken prior to dosing on Cycle 1 Day 1 only. Not applicable to patients enrolled in the expansion cohort.
f. PFTs only if your doctor feels this is needed
g. Serum pregnancy test
h: Urine pregnancy test every 4 weeks
i: Not applicable to patients enrolled in the expansion cohort.
j: If the patient has stable or responding disease at the end of 13 cycles of treatment (one year) and continues on daily Everolimus only, repeat the procedures performed for cycle 3 day 1 only every eight weeks (ie: Cycle 15 Day 1, Cycle 17 Day 1, Cycle 19 Day 1, etc.). Other visits are not required.

10.2 Serial imaging while on study treatment

The following imaging studies must be performed on the days and cycles indicated below.

- Tumor imaging including CT scan of the chest, abdomen, and pelvis or CT scan of the chest and MRI of the abdomen and pelvis at the end of cycle 2 (Day 28 ± 7 days), cycle 4 (Day 28 ± 7 days), and cycle 6 (Day 28 ± 7 days).

- From cycle 6 (24wks) through cycle 12 (48wks), imaging will be repeated every three cycles (every 12wks), i.e. at the end of cycle 9, and cycle 12 (Day 28 ± 7 days).
- After 12 cycles (48wks), imaging will be repeated every four cycles (every 16wks), i.e. at the end of cycle 16, 20, 24, etc. (Day 28 ± 7 days)
- Patients who cannot receive intravenous (IV) contrast will undergo imaging with CT chest without IV contrast and MRI of the abdomen/pelvis. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be performed should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to prior studies, if possible.
- Nuclear bone scans will be obtained in patients only if clinically indicated.

10.3 End of Study Treatment/Withdrawal Procedures

At the end of the study or at withdrawal, the following procedures should be performed within 28 days of last dose of either study medication:

- Physical examination including major body systems
- Karnofsky performance status, body weight, and vital signs
- Hematology: CBC, differential, platelets
- Blood Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin, LDH, sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, fasting glucose, lipid panel [patients must be fasting x 6h]
- Urine chemistry: Urinalysis will be performed for random protein and creatinine to calculate urine protein-creatinine ratio (UPCR).
- Tumor imaging including CT scan of the chest, abdomen, and pelvis or CT scan of the chest and MRI of the abdomen and pelvis and other applicable sites of disease (if not obtained in the prior cycle).
- Bone scan, if clinically indicated
- Assessment of adverse events and tumor-related signs and symptoms
- Assessment of study drug compliance/accountability. Subjects must return all used and unused medication/containers.

10.4 Post-Treatment Follow-Up

Subjects should continue to be evaluated for adverse effects of the study treatment up to 28 days after the last dose of study medication. At such post-treatment follow-up visits, the following procedures should be performed:

- Assessment of adverse events and tumor-related signs and symptoms
- Physical examination, Karnofsky performance status, laboratory assessments, or other tests necessary to follow unresolved or evaluate new adverse events

- Assessment of concomitant medications and treatments

During this period, the outcome of adverse events with a date of onset during the study period should be reevaluated, and any new adverse events should be recorded.

10.5 Correlative Studies

Biomarker discovery and validation will be performed to identify tumor biomarkers which may predict treatment response/failure to bevacizumab plus everolimus. Genomics correlations and immunohistochemical (IHC) analyses will be performed. First, to identify any potential correlations between histologic features and treatment response, we will conduct detailed histologic review of architectural and cytologic features of the tumors. In addition, to specifically elucidate the molecular basis of treatment response and resistance, standard IHC and scoring will be performed on archived paraffin tissue blocks to determine the underlying protein expression of key signaling molecules targeted by the treatment, including mTOR pathway activation markers phospho-S6 (p-S6) and phospho-4E BP1 (p-4E BP1); HIF pathway markers hypoxia inducible factor-1α (HIF-1α) and carbonic anhydrase IX (CA-IX); vascular maker CD31; and other key growth factors or regulators of interacting pathways such as platelet-derived growth factor receptor-β (PDGFR-β), phospho-AKT, and PTEN. Given the fact that the molecular underpinning of majority advanced ncRCC is largely unknown, the proposed IHC study is mainly limited to the pathways targeted by everolimus and bevacizumab.

To date (11/26/2013), emerging immunohistochemical (IHC) analysis on archived tumor samples is encouraging and thus far suggest that markers of mTOR pathway activation such as phospho-4E BP1 (p-4E BP1) are high in responders and low in non-responders.

Secondly, DNA extracted from tumors and matched normal tissue or blood specimens will be analyzed by the IMPACT assay, a targeted-exome capture assay with ultra-deep sequencing coverage (median 570x) using Illumina HiSeq 2000. This assay will identify genetic alterations within the genes most commonly genetically altered in cancer, which should shed considerable light upon why patients respond to the combined therapy. Genes that are within all pathways potentially targeted by everolimus and bevacizumab, such as MTOR, TSC1, TSC2, FLT1 (VEGFR1), and KDR (VEGFR2), will be additionally scrutinized at the raw sequence level, since we would expect to see alterations of these genes in responders given preliminary data in other responders to rapalog therapy.

Lastly, when additional tissues are available, additional studies, including gene-expression profiling, proteomics, and metabolomics will be performed.

11.1 TOXICITIES/SIDE EFFECTS

Individual toxicities previously reported for everolimus and bevacizumab, as well as adverse events seen in prior early phase trials combining everolimus and bevacizumab have been described in detail in sections 3.3.6, 3.3.3, and 3.3.10, respectively.

11.1 Severity assessment

The following definitions of Severity in accordance with Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE Version 4.03, Publish Date: June 14th, 2010 (Gompertz 1825)) to describe the maximum intensity of adverse events. If the event is serious (see section 17.2 for definition), the CTC grade reported and entered into the CRDB must be consistent with the description of CTC grade included in the narrative section of the serious adverse event report.

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances.)
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
4	Life-threatening consequences; urgent intervention indicated.
5	DEATH RELATED TO AE

A Semi-colon indicates „or" within the description of the grade. A single dash (-) indicates a grade is not available.

If required on SAE reporting forms, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	does not interfere with patient"s usual function
MODERATE	interferes to some extent with patient"s usual function
SEVERE	interferes significantly with patient"s usual function

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

11.2 Management of specific toxicities

11.2.1 Management of infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking Everolimus Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

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

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

11.2.2 Management of skin toxicity

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

11.2.3 Management of hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus.

11.2.4 Renal failure events

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

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

11.2.5 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. They should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 4.0 (Gompertz 1825) (see section 11.1).

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 Grade 2 toxicity, in which case patients have pain but are able to 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. For Grade 3 toxicity in which case patients cannot maintain adequate oral alimentation), Everolimus should be dose reduced. Everolimus should be discontinued if toxicity is a Grade 4.
4. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
5. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of everolimus metabolism, thereby leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

11.2.6 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 and will be obtained prior to study treatment initiation as well as once every two cycles while on treatment.

Grade 2 or 3 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) do not require dose modifications or interruption of treatment with everolimus, but should instead 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. As per section 6.1, these interventions are also indicated for patients with grade 2 or 3 cholesterol / triglyceride levels at the time of pre-treatment screening. Lipid lowering treatment tor these patients must be initiated prior to beginning study treatment. Patients with Grade 3 hypertriglyceridemia should be dose reduced one level.

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. Everolimus should be discontinued for development of Grade 4 hyperlipidemia.

Hyperglycemia has been reported in clinical trials. Fasting serum glucose will be assessed prior to the start of everolimus therapy and will be monitored while on treatment with fasting blood glucose checked every 2 cycles. Optimal glycemic control should be achieved before starting trial therapy and while on treatment using anti-hyperglycemic agents at the discretion of the individual investigator following the patient. See table 9.2 for everolimus dose modifications in the setting of treatment-related hyperglycemia.

11.2.7 Management of diarrhea

Appearance of diarrhea attributed to everolimus toxicity may be treated with loperamide.

11.2.8 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a known side effect of rapamycin analogues including everolimus. Clinically significant pneumonitis is typically accompanied by non-specific symptoms including dyspnea, nonproductive cough, fatigue, and fever. Diagnosis is generally suspected in individuals receiving mTOR inhibitors who develop these symptoms or in asymptomatic individuals in whom a routine chest CT scan reveals a new ground glass or alveolar infiltrate. The frequency of symptomatic pulmonary toxicity (all grades) was approximately 13% in a phase III study of everolimus in patients with metastatic renal cell carcinoma (Motzer, Escudier et al. 2008). Severe (CTC grade 3) pneumonitis occurred in 4% of patients, and an occasional fatality was reported. The lung toxicity was partly or completely reversible in the majority of cases with interventions including drug interruption, discontinuation and the use of corticosteroids. If non-infectious pneumonitis develops, consultation with a pulmonologist is recommended. Management of non-infectious pneumonitis suspected to be associated with everolimus and dose modification instructions are provided in table 11.1 and table 9.2 respectively.

Table 11.1 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1	CT scans with lung windows. Repeat at least every 3 cycles until return to within normal limits.	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. *	Consider corticosteroids if symptoms are 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. everolimus dose cannot be escalated.
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.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
	baseline. Bronchoscopy with biopsy and/or BAL is recommended if possible.		

* If a bronchoscopy is performed, then a biopsy and/or bronchoalveolar lavage is required.

11.2.9 Monitoring and prophylactic treatment for hepatitis B reactivation

Per MSKCC institutional policy for all patients undergoing anti-cancer therapy, all patients will be screened for hepatitis B prior to initiation of study treatment. HB Surface Antigen and HB core Antibody will be tested with HBV PCR performed reflexively for any abnormal results (see appendix). Patients with positive HB Surface Antigen or HBV PCR will be started on viral suppressive therapy with entecavir 0.5mg PO daily ≥ 1 week prior to the first dose of study drug. HBV DNA should be monitored periodically while on treatment. Treatment must continue throughout their treatment course with the study drugs and per MSKCC guidelines should be continued for at least six months after completion of treatment with everolimus and/or bevacizumab.

11.2.10 Management of hepatitis B reactivation

For hepatitis B reactivation definition and the management guidelines, see Table 11.2 Guidelines for management of hepatitis B.

Table 11.2 Guidelines for management of hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
For patients with baseline results: Positive HBV-DNA OR positive HBs Ag ---------- reactivation is defined as: [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA] AND ALT elevation x 5 ULN	Treat: Start a second antiviral AND Interrupt study drug administration until resolution: ≤ grade 1 ALT (or baseline ALT, if > grade 1) and ≤ baseline HBV-DNA levels If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. (see Table 9.1 – Dose reduction steps for everolimus) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue both antiviral therapies at least 4 weeks after last dose of study drug.
For patients with baseline results: Negative HBV-DNA and HBsAg	Treat : Start first antiviral medication AND Interrupt study drug administration until resolution: ≤ baseline HBV-DNA levels

AND [Positive HBs Ab (with no prior history of vaccination against HBV), OR positive HBc Ab] ---------- reactivation is defined as: New appearance of measurable HBV-DNA	If resolution occurs within ≤ 28 days study drug should be re-started at one dose lower, if available. (see Table 9.1 – Dose reduction steps for everolimus) If the patient is already receiving the lowest dose of study drug according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of study drug. If resolution occurs > 28 days Patients should discontinue study drug but continue antiviral therapy at least 4 weeks after last dose of study drug.

* All reactivations of hepatitis B are to be recorded as grade 3 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation), unless considered life threatening by the investigator; in which case they should be recorded as grade 4 (CTCAE v 4.0 Metabolic Laboratory/Other: Viral Re-activation) . Date of viral reactivation is the date on which both DNA and ALT criteria were met (e.g. for a patient who was HBV-DNA positive on 01-JAN-10 and whose ALT reached ≥ 5 × ULN on 01-APR-10, the date of viral reactivation is 01-APR-10).

11.2.11 Guidelines for management of hepatitis C reactivation

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

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

For definitions of HCV flare and actions to be taken in the event of a flare, please refer to Table 11.3.

Table 11.3 Guidelines for the management of hepatitis C flare

Baseline results	HCV flare definition*	HCV flare management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue Everolimus

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above

were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

11.2.12 Management of gastrointestinal perforation

Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation.

An adverse event of gastrointestinal perforation, irrespective of causal relationship, should be reported throughout the course of the study and during the 6 month follow-up period.

11.2.13 Management of surgical procedures/wound-healing complications

Bevacizumab should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound-healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. Bevacizumab should be withheld for elective surgery.

11.2.14 Management of hypertension

Patients should be monitored for the development or worsening of hypertension via frequent blood pressure measurement. Temporary suspension of bevacizumab is recommended in patients with evidence of severe hypertension that is not controlled with medication. Hypertension is to be treated with appropriate anti-hypertensive therapy. See Table 11-4 for management of hypertension.

Table 11.4 Management of Hypertension

Worst Grade Hypertension	Definition	Action
Grade 1	Asymptomatic, transient (< 24 hours) increase by >20 mmHg diastolic or to > 140/90 mmHg if previously within normal limits	Intervention is not indicated.
Grade 2	Symptomatic increase by > 20 mmHg (diastolic) or to >140/90mm Hg if previously within normal limits; recurrent or persistent (> 24 hours)	Monotherapy of anti-hypertensive may be indicated. Once controlled and stable <150/100 mmHg, patients may continue bevacizumab treatment.
Grade 3	Requiring more than one anti-hypertensive or more intensive therapy than previously:	Bevacizumab should be withheld for persistent or symptomatic hypertension and should be permanently discontinued if hypertension is not controlled.
Grade 4	Life threatening consequences (e.g., hypertensive crisis)	Occurrence of Grade 4 hypertension should lead to permanent discontinuation of bevacizumab. All doses of anti-hypertensive medicines should be recorded at all visits.

11.2.15 Management of Proteinuria

While receiving bevacizumab, patients will be monitored for the occurrence of significant proteinuria. All patients will have a dipstick urinalysis performed at the beginning of every other cycle, i.e. prior to every fourth bevacizumab dose. For ≥2+ proteinuria on dipstick, reflective quantification of proteinuria will be performed by determination of the urine protein-creatinine ratio (UPCR). The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection (Ginsberg, Chang et al. 1983; Schwab, Christensen et al. 1987; Rodby, Rohde et al. 1995). Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24 hour urine collection. For this purpose, at least 4 ml of a random urine sample will be collected in a sterile container (this does not have to be a 24-hour urine). Samples will be analyzed for random urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as follows: protein concentration (mg/dL)/creatinine (mg/dL).
Management in regards to further administration of bevacizumab will be determined as follows:

- < 2+ proteinuria (dipstick): administer bevacizumab as planned.
- ≥ 2+ proteinuria (dipstick): determination of urine protein-creatinine ratio (UPCR)
  - UPC ratio < 2.0 Continue bevacizumab.
  - UPC ratio ≥ 2.0 Hold bevacizumab until UPC ratio recovers to < 2.0 (recheck every other week).
  - If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab.
  - nephrotic syndrome: Discontinue bevacizumab

Table 11.5 Management of proteinuria

UPC ratio < 2.0	Continue bevacizumab
UPC ratio ≥ 2.0	Hold bevacizumab until UPC ratio recovers to < 2.0 (recheck every other week)
nephrotic syndrome	Discontinue bevacizumab

11.2.16 Management of thrombosis/embolism

All toxicity will be graded according to the CTCAEv4.0 guidelines. For management decisions in the setting o thromboembolic events, see table 11.5.

Table 11.6 Management of thrombosis / embolism

Event	Action
Arterial thromboembolic event	Discontinue bevacizumab permanently
Grade 3 or 4 venous thrombosis	Hold bevacizumab for 2 weeks. Bevacizumab may be resumed after initiation of therapeutic-dose anticoagulant therapy as soon as all of the following criteria have been met: The patient must be on a stable dose of anticoagulant, and if on warfarin, the patient must have an INR within the target range (usually between 2 and 3) prior to restarting bevacizumab. The patient must not have had a Grade 3 or 4 hemorrhagic event

Event	Action
	since entering the study. The patient must not have had any evidence of tumor invading or abutting major blood vessels on any prior disease assessment. Blood samples should be taken prior to initiation of treatment for the following lab values: INR, PTT, PT, D-dimers, anti-thrombin III.
Symptomatic Grade 4 thrombosis	Discontinue patient from study

11.2.17 Management of Hemorrhage

All toxicity will be graded according to the CTCAEv4.0 guidelines. Patients who develop ≥ Grade 3 hemorrhage should discontinue bevacizumab.

11.2.18 Infusion Reactions

Infusion reactions reported in prior clinical trials include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. Reactions with the first dose of bevacizumab are uncommon (<3%) and severe reactions have been reported in 0.2% of patients.

If a severe infusion reaction occurs, infusion should be stopped and appropriate medical therapy should be administered. Treatment can be continued with premedication for subsequent cycles at the investigator"s discretion.

11.8 Laboratory Safety Assessments

Blood:

- Hematology, Coagulation, and Blood Chemistry samples will be drawn at the time points described in Sections 8.0 and 10.0. Additional blood tests may be performed for the purposes of planning treatment administration, dose modification, or following adverse events.

- Fasting blood glucose. The patient must be in a fasting state (at least 6 hours) at the time of blood sampling for this evaluation.

- Serum pregnancy test for women of childbearing potential will be performed prior to administration of the first dose of study treatment (results must be available for eligibility determination).

- Lipid panel: A serum lipid profile includes: total cholesterol, triglycerides, LDL, and HDL. The patient must be in a fasting state (at least 6 hours) at the time of blood sampling for this evaluation.

Urine:

- Urinalysis will be performed periodically for detection of elevated urine protein excretion. Should such elevation be seen, 24 hour urine collection or urine collection for UPCR will be necessary, as outlined in sections 6.2 and 11.2.10, respectively.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The determination of antitumor efficacy will be based on objective tumor assessments made according to the RECIST1.1(Eisenhauer, Therasse et al. 2009) system of unidimensional evaluation and treatment decisions by the investigator will be based on these assessments. A minor modification will be adopted to accommodate standard practice in use of spiral CT scan (i.e., reconstruction interval up to 8 mm). In the event spiral CT scan is used to assess tumors, minimum lesion size qualifying as measurable should be twice the reconstruction interval used and at least 10 mm.

The same method and technique should be used to characterize each identified and reported lesion at baseline, during the study treatment period, and during the follow-up period. Imaging-based evaluation over clinical examination is the required technique when both could be used to assess the antitumor effect of the treatment. CT or MRI scan are the preferred methods for the tumor assessment.

For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be performed should also be based on tumor type, anatomic location of the disease and should be optimized to allow for comparison to prior studies if possible.

Whenever possible, clinical evaluation of superficial lesions should not be used as the sole form of measurement. However, when necessary, color photograph with metric caliber is acceptable. Tumor evaluation by positron emission tomography (PET) scan or by ultrasound may not substitute for CT or MRI scans.

Radiologic tumor assessments will be performed at screening, at the end of the dosing period of cycles as outlined in Section 10 and whenever disease progression is suspected. After the patient is withdrawn from study treatment, another tumor assessment will be performed if an assessment has not been performed within the prior 6 weeks.

12.1 Calculated Endpoint Definitions

12.1.1 Progression free survival (PFS)

PFS will be defined as the duration of time from enrollment until death or progression of disease. Patients still progression free at the time of analysis will be considered censored.

12.1.2 Objective response rate (ORR)

- Overall confirmed objective response rate (ORR), defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR)

according to the RECIST1.1 criteria (Eisenhauer, Therasse et al. 2009), relative to the total population of patients who receive at least one dose of study drug. Confirmed responses are those that persist on repeat imaging study ≥ 4 weeks after initial documentation of response.

13.1 CRITERIA FOR REMOVAL FROM STUDY

13.2 Study treatment discontinuation

If both medications have to be interrupted for more than 21 days (>4 weeks for hepatitis B reactivation), the patient will be discontinued from the study.

The patient may discontinue study treatment for any of the following reasons:

- Adverse event(s) as specified in sections 9.3 and 11.2
- Subject withdrew consent
- Lost to follow-up
- Administrative problems
- Disease progression
- Protocol deviation
- Discretion of the Investigator

If a patient has discontinued the study treatment due to an unacceptable adverse drug reaction or an abnormal laboratory value, he/she should not have withdrawal of consent recorded as the reason for discontinuation. Instead, the reason for discontinuation must be recorded as due to adverse drug reaction or an abnormal laboratory value.

14.1 BIOSTATISTICS

14.2 Study design / Primary endpoint

The purpose of this study is to assess the efficacy of everolimus plus bevacizumab in patients with metastatic non-clear cell RCC. The primary endpoint is the percent of patients alive and progression-free after 6 months of therapy.

This study is designed as a single-stage, phase II trial which requires a total of 34 patients. If 22 or more patients are progression-free after 6 months from the first day of treatment, this regimen will be considered feasible and will merit further clinical study. With 34 patients, this design discriminates between true response rates of ≤ 50% and ≥ 70% at a Type I error of 6% and a Type II error of 19%. Our null hypothesis of 50% was chosen based on phase II data in non-clear cell RCC from our center showing a PFS of 50% at 6 months with single agent sunitinib in the first-line setting(Molina, Feldman et al. 2010). While sunitinib is not part of this regimen, this is the only prospective data for targeted therapy in this group of kidney cancer subtypes available for comparison.

Patients that come off study before 6 months before documented progression/death will be treated as events for the 6 month PFS endpoint. In addition to counting the number of patients alive and progression-free at 6 months, a Kaplan-Meier curve will be calculated for

progression-free survival. All patients will be used in the analysis. Patients still progression free at the time of analysis will be considered censored. Median progression-free survival (and 95% confidence interval) will be determined from that curve. In addition to counting the number of patients alive and progression-free at 6 months, a Kaplan-Meier curve will be calculated for progression-free survival. Patients still progression free at the time of analysis will be considered censored. Median progression-free survival (and 95% confidence interval) will be determined from that curve.

To date (11/26/2013), the study has enrolled 32 patients (5 chromophobe, 2 medullary, 7 papillary, 11 unclassified and 7 unclassified with papillary features). Preliminarily, 5/6 patients with papillary and 3/6 patients with unclassified (papillary features) have met the study"s primary endpoint of progression-free after 6 months of therapy. Three out of six patients with papillary RCC achieved a partial response (PR) as best response. Two out of six patients with unclassified with papillary features achieved a PR as best response (1 is unconfirmed). Additionally, 4 patients (2 papillary and 2 unclassified with papillary features) have stable disease beyond 14 and 11 months, respectively. The preliminary efficacy results are extremely encouraging for this subgroup of patients who traditionally experience modest responses to targeted agents.

Based on these extremely encouraging preliminary results and the lack of a standard of care for these rare kidney tumors, we will accrue a separate cohort of patients with non-clear cell RCC with papillary features. We expect to see a total of approximately 10 patients per year with non-clear cell RCC with papillary features. We anticipate this will take two years but will continue past this point if necessary to accrue all 20 patients. The efficacy of treatment in this cohort will be analyzed descriptively. They will be studied separately in secondary analyses and will have no effect of analysis of the study"s main objective.

14.3 Sample Size / Accrual Rate

The total planned sample size is 54 patients. An estimated 10 patients with non-clear cell RCC with papillary features are seen at MSKCC per year. Considering this, estimated time to accrue an additional 20 patients is two years. Following completion of accrual, an additional 6 months is estimated for follow-up.

14.4 Analysis of secondary endpoints

Secondary endpoints include objective response rate, the safety of the drug combination in this population and the assessment of expression of correlative biomarkers.

14.4.1 Objective response rate (ORR)

Response will be evaluated by use of the international criteria as defined by the Response Evaluation Criteria in Solid Tumors Committee (RECIST 1.1) (Eisenhauer, Therasse et al. 2009). All responses will be confirmed ≥ 4 weeks after initial documentation of response. Response rates and 95% confidence interval will be estimated using exact binomial methods.

14.4.2 Safety of the study drug combination in the study population

Toxicity will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (Gompertz 1825), as outlined in section 11.5. Toxicities will be summarized by type and grade using frequencies and rates.

14.4.3 Correlative biomarkers

Expression levels of phospho-Akt, phospho-S6, HIF-1α, and PTEN in pretreatment patient tumor samples will be assessed with aim of correlating levels to treatment benefit. In evaluating the correlative endpoints to this study, Fisher"s exact test will be employed to determine, whether the biomarkers are predictive for treatment response in the studied drug combination. Logistic regression will be used to relate 2 or 3 biomarkers to response simultaneously.

In evaluating the correlative markers for the combined everolimus and bevacizumab treatment, two-sided Fisher"s exact test will be employed to determine whether the biomarkers are predictive for treatment response in the studied drug combination. A Kaplan-Meier curve will be calculated for progression-free survival related to specific biomarkers or combinations of biomarkers.

Multivariate analyses with age, gender, tumor size, histological subtype, and grade will be performed. Pearson correlation, Chi-square tests, Student"s *t* test, univariable and multivariable Cox regression analysis, hazard ratios, Kaplan-Meier curves, and log-rank test will all be used to calculate significant association of biomarkers with clinical results and determine if the biomarkers are indeed predictive.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

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

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

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

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

15.3 Randomization

N/A – no randomization in this study.

16.1 DATA MANAGEMENT ISSUES

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

The data collected for this study will be entered into a secure database. Source documents will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team.

16.3 Data and Safety Monitoring

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

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

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

17.1 PROTECTION OF HUMAN SUBJECTS

The risks, benefits and objectives of the study will be reviewed with each participant prior to enrollment. Patients will be made aware of the voluntary nature of this trial, potential adverse

effects of the study treatment, alternative treatment options, and financial costs associated with treatment on this trial. Written informed consent will then be obtained prior to enrollment. Privacy and confidentiality will be maintained for all participants, and the study is designed with careful monitoring of toxicity through physician visits and laboratory assessment to assure patient safety.

17.2 Privacy

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

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject"s initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

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

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

17.2.1 SAE reporting to Novartis

All SAEs, regardless of suspected causality, that occur within 30 days of the last intervention or the last dose/treatment with the investigational agent/product must be reported to Novartis. Any SAEs experienced after this period should only be reported to Novartis only if the investigator suspects a causal relationship to the study treatment. The completed, signed form will be faxed (877-778-9739) within 24 hours to the Novartis Drug Safety and Epidemiology Department. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 5 business days 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 event should be reported separately as a new event.

17.3 Pregnancy and assessments of fertility

Pregnancy testing is required at screening and recommended monthly until the end of the trial. Serum pregnancy testing should be performed at screening and at the end of the study. Urine pregnancy testing should be performed at each visit (every 4 weeks).

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects including embryo-toxicity and feto-toxicity. The potential risk for humans is unknown. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus. If a female becomes pregnant while on study treatment, the newborn will be followed for at least 12 months.

It is not known whether everolimus is excreted in breast milk. However, in animal studies everolimus and/or its metabolites readily passed into the milk of lactating rats. Women taking everolimus should therefore not breast-feed.

17.3.1 Women of childbearing potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment. Highly effective contraception is defined as either:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
- Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study, the vasectomised male partner should be the sole partner for that subject].
- Use of a combination of any two of the following (a+b or a+c or b+c):
  a. Use of oral, injected, implanted or other hormonal methods of contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
- In case of use of oral contraception, women should have been stable on the oral agent before taking study treatment.

17.3.2 Male Contraception

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

17.3.3 Fertility

The potential for everolimus to cause infertility in male and female patients is unknown.

However, menstrual irregularities, secondary amenorrhea and associated luteinizing hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed.

Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus.

17.3.4 Pregnancy

Preclinical data regarding reproductive toxicity is described in the most recent Investigator Brochure. The potential reproductive risk for humans is unknown. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must 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. The newborn will be followed for at least 12 months.

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

17.4 Cost

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include the cost of bevacizumab, hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG and doctor"s fees. However, the sponsor, Novartis International AG, will supply everolimus at no cost to the patient. Patients will not be charged for the correlative studies included in this trial.

18.1 INFORMED CONSENT PROCEDURES

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

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

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

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

19.0 REFERENCES

Agarwala, S. S. and S. Case (2010). "Everolimus (RAD001) in the treatment of advanced renal cell carcinoma: a review." Oncologist **15**(3): 236-245.

Amin, M. B., P. Tamboli, et al. (2002). "Prognostic impact of histologic subtyping of adult renal epithelial neoplasms: an experience of 405 cases." Am J Surg Pathol **26**(3): 281-291.

Awada, A., A. Hendlisz, et al. (2005). "Phase I safety and pharmacokinetics of BAY 43-9006 administered for 21 days on/7 days off in patients with advanced, refractory solid tumours." Br J Cancer **92**(10): 1855-1861.

Azim, H., H. A. Azim, Jr., et al. (2010). "Targeting mTOR in cancer: renal cell is just a beginning." Target Oncol.

Beck, S. D., M. I. Patel, et al. (2004). "Effect of papillary and chromophobe cell type on disease-free survival after nephrectomy for renal cell carcinoma." Ann Surg Oncol **11**(1): 71-77.

Bendell, J. C., D. Gerorge, et al. (2007). "Results of a phase I study of bevacizumab (BV), everolimus (EV), and erlotinib (E) in patients with advanced solid tumors." J Clin Oncol **25**(18s (abstract 3548)).

Bertoni, F., C. Ferri, et al. (1987). "Sarcomatoid carcinoma of the kidney." J Urol **137**(1): 25-28.

Bjornsti, M. A. and P. J. Houghton (2004). "The TOR pathway: a target for cancer therapy." Nat Rev Cancer **4**(5): 335-348.

Cheung, V. G., M. Morley, et al. (199). "Making and reading microarrays." Naure Genet **21**: 15-19.

Cheville, J. C., C. M. Lohse, et al. (2003). "Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma." Am J Surg Pathol **27**(5): 612-624.

Cho, D., S. Signoretti, et al. (2007). "Potential histologic and molecular predictors of response to temsirolimus in patients with advanced renal cell carcinoma." Clin Genitourin Cancer **5**(6): 379-385.

Choueiri, T. K., R. M. Bukowski, et al. (2006). "The current role of angiogenesis inhibitors in the treatment of renal cell carcinoma." Semin Oncol **33**(5): 596-606.

Choueiri, T. K., A. Plantade, et al. (2008). "Efficacy of sunitinib and sorafenib in metastatic papillary and chromophobe renal cell carcinoma." J Clin Oncol **26**(1): 127-131.

Dutcher, J. P., P. de Souza, et al. (2009). "Effect of temsirolimus versus interferon-alpha on outcome of patients with advanced renal cell carcinoma of different tumor histologies." Med Oncol **26**(2): 202-209.

Eisenhauer, E. A., P. Therasse, et al. (2009). "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer **45**(2): 228-247.

Escudier, B., J. Bellmunt, et al. (2010). "Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival." J Clin Oncol **28**(13): 2144-2150.

Escudier, B., T. Eisen, et al. (2007). "Sorafenib in advanced clear-cell renal-cell carcinoma." N Engl J Med **356**(2): 125-134.

Escudier, B., A. Pluzanska, et al. (2007). "Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial." Lancet **370**(9605): 2103-2111.

Escudier, B., A. Ravaud, et al. (2008). "Update on AVOREN trial in metastatic renal cell carcinoma (mRCC): Efficacy and safety in subgroups of patients (pts) and pharmacokinetic (PK) analysis." Journal of Clinical Oncology **26**(May 20 suppl (abstr 5025)).

Feldman, D. R., M. S. Baum, et al. (2009). "Phase I trial of bevacizumab plus escalated doses of sunitinib in patients with metastatic renal cell carcinoma." J Clin Oncol **27**(9): 1432-1439.

Ferlay, J., H. R. Shin, et al. (2010). "Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008." Int J Cancer.

Fischer, P., P. Patel, et al. (2008). "Phase I study combining treatment with temsirolimus and sunitinib malate in patients with advanced renal cell carcinoma." J Clin Oncol **26 (suppl; abstr 16020)**.

Flanigan, R. C., S. E. Salmon, et al. (2001). "Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer." N Engl J Med **345**(23): 1655-1659.

Fossa, S. D. (2000). "Interferon in metastatic renal cell carcinoma." Semin Oncol **27**(2): 187-193.

Fyfe, G., R. I. Fisher, et al. (1995). "Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy." J Clin Oncol **13**(3): 688-696.

Ginsberg, J. M., B. S. Chang, et al. (1983). "Use of single voided urine samples to estimate quantitative proteinuria." N Engl J Med **309**(25): 1543-1546.

Gnarra, J. R., K. Tory, et al. (1994). "Mutations of the VHL tumour suppressor gene in renal carcinoma." Nat Genet **7**(1): 85-90.

Gompertz, G. (1825). "On the nature of the function expressive of the law of human of human mortality, and on the new mode of determining the value of life contingencies." **115**: 513-585.

Hainsworth, J. D., D. R. Spigel, et al. (2010). "Phase II trial of bevacizumab and everolimus in patients with advanced renal cell carcinoma." J Clin Oncol **28**(13): 2131-2136.

Heng, D. Y. and T. K. Choueiri (2009). "Non-clear cell renal cancer: features and medical management." J Natl Compr Canc Netw **7**(6): 659-665.

Higuchi, R., C. Fockler, et al. (193). "Kinetic PCR analysi: reaql-time monitoring of DNA amplification reactions." Biotechnology **11**: 1026-1030.

Hudes, G., M. Carducci, et al. (2007). "Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma." N Engl J Med **356**(22): 2271-2281.

Ikezoe, T., C. Nishioka, et al. (2006). "The antitumor effects of sunitinib (formerly SU11248) against a variety of human hematologic malignancies: enhancement of growth inhibition via inhibition of mammalian target of rapamycin signaling." Mol Cancer Ther **5**(10): 2522-2530.

Ikezoe, T., Y. Yang, et al. (2006). "Effect of SU11248 on gastrointestinal stromal tumor-T1 cells: enhancement of growth inhibition via inhibition of 3-kinase/Akt/mammalian target of rapamycin signaling." Cancer Sci **97**(9): 945-951.

Jacobsen, J., K. Grankvist, et al. (2006). "Different isoform patterns for vascular endothelial growth factor between clear cell and papillary renal cell carcinoma." BJU Int **97**(5): 1102-1108.

Jemal, A., R. Siegel, et al. (2010). "Cancer Statistics, 2010." CA Cancer J Clin.

Kourda, N., A. Zeddini, et al. (2006). "Sarcomatoid renal cell carcinoma in a young adult." Pathologica **98**(3): 181-183.

Kovacs, G., M. Akhtar, et al. (1997). "The Heidelberg classification of renal cell tumours." J Pathol **183**(2): 131-133.

Kroog, G. S., D. R. Feldman, et al. (2009). "Phase I trial of RAD001 (everolimus) plus sunitinib in patients with metastatic renal cell carcinoma." J Clin Oncol **27**(15s (abstr 5037)).

Kulke, M., H. J. Lenz, et al. "A phase 2 study to evaluate the efficacy and safety of SU11248 in patients (pts) with unresectable neuroendocrine tumors (NETs). (Oral presentation). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Mai, K. T., D. C. Landry, et al. (2001). "A comparative study of metastatic renal cell carcinoma with correlation to subtype and primary tumor." Pathol Res Pract **197**(10): 671-675.

Maki, R. G., J. A. Fletcher, et al. "SU11248 in patients with imatinib-resistant GIST: results from a continuation trial. (Oral presentation). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Manning, B. D. and L. C. Cantley (2007). "AKT/PKB signaling: navigating downstream." Cell **129**(7): 1261-1274.

Miller, K. D., H. J. Burstein, et al. "Phase II study of SU11248, a multitargeted receptor tyrosine kinase inhibitor (TKI), in patients (pts) with previously treated metastatic breast cancer (MBC). (Oral presentation). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Moch, H., T. Gasser, et al. (2000). "Prognostic utility of the recently recommended histologic classification and revised TNM staging system of renal cell carcinoma: a Swiss experience with 588 tumors." Cancer **89**(3): 604-614.

Molina, A. M., D. R. Feldman, et al. (2010). "Phase II trial of sunitinib in patients with metastatic non-clear cell renal cell carcinoma." Invest New Drugs **in press (accepted July 07 2010)**.

Motzer, R. J., J. Bacik, et al. (2002). "Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology." J Clin Oncol **20**(9): 2376-2381.

Motzer, R. J., B. Escudier, et al. (2008). "Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial." Lancet **372**(9637): 449-456.

Motzer, R. J., T. E. Hutson, et al. (2007). "Sunitinib versus interferon alfa in metastatic renal-cell carcinoma." N Engl J Med **356**(2): 115-124.

Motzer, R. J., M. D. Michaelson, et al. (2006). "Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma." J Clin Oncol **24**(1): 16-24.

Norden-Zfoni, A., J. Manola, et al. "Levels of cirulating endothelial cells and monocytes as pharmacodynamic markers of SU11248 activity in patients with metastatic imatinib-resistant GIST. (Oral presentation). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Pantuck, A. J., D. B. Seligson, et al. (2007). "Prognostic relevance of the mTOR pathway in renal cell carcinoma: implications for molecular patient selection for targeted therapy." Cancer **109**(11): 2257-2267.

Patard, J. J., E. Leray, et al. (2005). "Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience." J Clin Oncol **23**(12): 2763-2771.

Plimack, E. R., E. Jonasch, et al. (2010). "Sunitinib in papillary renal cell carcinoma (pRCC): Results from a single-arm phase II study." Journal of Clinical Oncology **28**(15s (abstr 4604)).

Pollack, J. R., C. Perou, et al. (199). "Genome-wide analysis of DNA copy-number changes using cDNA microarrays." Nature **23**: 41-46.

Posada, E. M., J. Gulley, et al. "A phase II study of BAY 43-9006 in patients with androgen-independent prostate cancer (AIPC) with proteomic profiling. (Oral presentation). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Ravaud, A., S. Oudard, et al. (2009). "First-line sunitinib in type I and II papillary renal cell carcinoma (PRCC): SUPAP, a phase II study of the French Genito-Urinary Group (GETUG) and the Group of Early Phase trials (GEP)." J Clin Oncol **27**(15s (suppl; abstr 5146)).

Reuter, V. E. and J. C. Presti, Jr. (2000). "Contemporary approach to the classification of renal epithelial tumors." Semin Oncol **27**(2): 124-137.

Rodby, R. A., R. D. Rohde, et al. (1995). "The urine protein to creatinine ratio as a predictor of 24-hour urine protein excretion in type 1 diabetic patients with nephropathy. The Collaborative Study Group." Am J Kidney Dis **26**(6): 904-909.

Rudloff, J., A. Boulay, et al. "The mTOR pathway in estrogen response: a potential for combining the rapamycin derivative RAD001 wih the aromatase inhibitor letrozole (Femara) in breast carcinoma. Proc Am Assoc Cancer Res 2004; 45: abstract."

Schwab, S. J., R. L. Christensen, et al. (1987). "Quantitation of proteinuria by the use of protein-to-creatinine ratios in single urine samples." Arch Intern Med **147**(5): 943-944.

Smeraglia, J. "Bioanalytical method validation life cycle for the measurement of SU011248, and metabolites SU012662 and SU012487 in human plasma. (Oral presentation) 16th International Reid Bioanalytical Forum, England, July 2005.".

Steinbild, S., F. Baas, et al. "Phase I study of BAY 43-9006 (sorafenib), a Raf kinase and VEGFR inhibitor, combined with irinotecan (CPT-11) in advanced solid tumors. (Abstract 3115). American Society of Clinical Oncology 41st Annual Meeting, Orlando, Florida, USA, 13-17 May, 2005. Available at: **Error! Hyperlink reference not valid.**.

Sternberg, C. N., I. D. Davis, et al. (2010). "Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial." J Clin Oncol **28**(6): 1061-1068.

Wang, L., T. E. Harris, et al. (2007). "PRAS40 regulates mTORC1 kinase activity by functioning as a direct inhibitor of substrate binding." J Biol Chem **282**(27): 20036-20044.

Witzig, T. E., S. M. Geyer, et al. (2005). "Phase II trial of single-agent temsirolimus (CCI-779) for relapsed mantle cell lymphoma." J Clin Oncol **23**(23): 5347-5356.

Wullschleger, S., R. Loewith, et al. (2006). "TOR signaling in growth and metabolism." Cell **124**(3): 471-484.

Yang, J. C., L. Haworth, et al. (2003). "A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer." N Engl J Med **349**(5): 427-434.

20.0 APPENDICES

Appendix 1: MSKCC standard for screening and treatment of HBV

Appendix 2: Package Insert Bevacizumab

Appendix 3: Package Insert Everolimus