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STUDY TITLE: **A Phase II Study of Alternative Sunitinib Scheduling in Patients with Metastatic Renal Cell Carcinoma (mRCC)**

SUPPORTER: Pfizer, Inc.

AGENT: Sunitinib malate

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1.0 INTRODUCTION

1.1 Metastatic Renal Cell Carcinoma

The estimated incidence of cancers of the kidney and renal pelvis in the United States is approximately 65,000 new cases in 2013, resulting in 13,680 deaths [1]. Renal cell carcinoma has historically presented physicians with many challenges. The often asymptomatic and clinically occult course of RCC has made it a difficult malignancy to diagnose resulting in a large proportion of patients being diagnosed with advanced or metastatic renal cell carcinoma (mRCC) [2]. In addition, prior studies have shown mRCC to be one of the most treatment-resistant solid tumors in oncology. Cytoreductive surgery and cytotoxic chemotherapy have shown limited effectiveness [3-5]. Immunotherapy has had better results, although response rates are still low and treatment is highly toxic [6-11]. The VHL-HIF pathway is pivotal to the pathobiology of RCC, and has been crucial in the development of targeted agents that include VEGFR inhibitors as well as antibodies to circulating VEGF. Furthermore, mammalian target of rapamycin (mTOR) molecules that are downstream of phosphoinositide 3-kinase and protein kinase B pathways have also demonstrated an increased concentration of HIF-alpha; thus, playing a significant role in angiogenesis [12]. Thus, the therapeutic landscape of mRCC has changed dramatically since 2005, with significant increases in overall survival [13]. This has subsequently resulted in the establishment of these agents as a first-line standard for patients with mRCC [14]. Despite their efficacy, these agents continue to be the focus of ongoing investigation, attempting to identify the best therapeutic regimen to maximize response and minimize toxicity.

1.2 Balancing toxicity with efficacy

Sunitinib, an oral inhibitor of vascular endothelial growth factor receptor (VEGFR) 1, 2, 3 and platelet derived growth factor receptor (PDGFR), has demonstrated prolongation of median progression free survival (PFS) in a large phase III study of patients with mRCC [6]. This led to FDA approval in 2006 and sunitinib has become a standard of care in front line treatment of mRCC.

There is emerging evidence that supports the association of relative dose intensity (RDI) of antiangiogenic agents with improvement in response rates and treatment efficacy [15, 16]. Houk et al. conducted a retrospective pharmacologic analysis across six trials of sunitinib, and determined that patients with the highest drug exposure experience longer overall survival, longer time to progression, and greater tumor reduction [15]. As can be expected, tentative relationships were also identified between total drug exposure and the incidence of fatigue, reduction in neutrophil counts and diastolic hypertension.

While the therapeutic goal in the treatment of mRCC is prolongation of survival, it is important to keep treatment related toxicities to a minimum. In real-world practice, maintenance of dose intensity of sunitinib can be challenging due to treatment-related adverse effects, including fatigue, hypertension, hand-foot syndrome (HFS) and diarrhea. In the original phase III trial, for instance, 38% and 32% of patients in the sunitinib arm underwent dose interruptions and reductions respectively, secondary to toxicities [6]. The impact of treatment related toxicities on patients can be significant, and for some patients, living longer may not always equate with living better. Wong et al. offered an interesting

insight into this, by quantifying preferences in patients with RCC who completed a survey with hypothetical treatment choice questions [17]. Their study revealed that fatigue and diarrhea were the most troublesome toxicities for patients, and that to reduce severe fatigue to mild-to-moderate fatigue, patients would be willing to forego 4.4 months of PFS. Interestingly, at the standard schedule of treatment for 4 weeks followed by a 2 week break (schedule 4/2), a cyclic scoring pattern is observed in patient reported quality of life indicators; with improvement in mean scores after the 2 week treatment break (i.e., between day 28 and day 42 scores) [18].

More recently, patient preferences for sunitinib versus active comparators were evaluated in randomized trials, results of which were presented at ESMO 2012. Data from the double blind cross-over PISCES trial comparing patient preferences between sunitinib and pazopanib, revealed that patient reported functional assessments of quality of life favored pazopanib over sunitinib with respect to fatigue, soreness of hands, feet and mouth [19]. Additionally, the phase III randomized COMPARZ study also highlighted differences in quality of life domains, which favored pazopanib over sunitinib [20]. Individual toxicities reported from this study are depicted in section 1.5. Thus, optimization of sunitinib administration is needed to maintain daily dose but to decrease the incidence of troublesome toxicity.

1.3 Sunitinib

1.3.1 Molecular formula and chemical name

Sunitinib is a small molecule with the molecular formula C22H27FN4O2. The free base has a molecular weight of 398.48 and the L-malate salt has a molecular weight of 532.57. The chemical name of the L-malate salt is 5-(5-fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2,4-dimethylpyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide
compound with (S)-2-hydroxy-succinic acid 1:1.

1.3.2 Preclinical Data

Sunitinib is a potent inhibitor of the tyrosine kinase activity of the split-kinase domain receptor tyrosine kinases (RTKs) VEGFR2 and PDGFR, which are involved in angiogenesis, as well as for the RTKs, KIT, a receptor for stem cell factor (SCF), and FLT3 that are involved in certain solid tumors and hematological malignancies [21-24]. Sunitinib inhibits the ligand-dependent tyrosine phosphorylation of target RTKs and the in vitro mitogenic response of human umbilical vein endothelial cells (HUVECs) stimulated with VEGF or FGF, of PDGFR-expressing NIH-3T3 cells stimulated with PDGF, and of MO7E acute myeloid leukemia cells stimulated with SCF. In subcutaneous (SC) xenograft tumor models, oral administration of sunitinib results in potent inhibition of tumor growth, causing regression or stasis of large established tumors of multiple origins. The antitumor activity of sunitinib is associated with its ability to reduce tumor microvessel density in established tumors thereby acting as an inhibitor of tumor angiogenesis. Sunitinib also inhibits the growth of tumor metastases as indicated by its ability to inhibit lung colonization with B16-F1 tumor cells injected into the tail vein of athymic mice.

1.3.3 Animal studies

See the Investigator's Brochure for full details. In summary, the toxicology and toxicokinetic data from studies in monkeys indicated that sunitinib treatment for up to 4 weeks with a 2-week treatment rest period (repeated cycles) was well tolerated at the dose level of 6 mg/kg/day without progression in lesion incidence and severity in the second cycle. Accumulation of sunitinib or its active metabolite was not observed in the cycling regimen indicating that plasma steady state was attained within 28 days of dosing. Similar plasma and tissue exposure is anticipated following repeated cycles of dosing. Through routine clinical monitoring, sunitinib-related adverse outcomes in animals were easily identifiable and reversible and were thus believed to be readily manageable in humans.

1.3.4 Clinical Data

The clinical safety and efficacy of sunitinib has been studied in 15 phase 1 and 2 clinical trials. Dose escalation phase 1 studies were designed to determine the primary dose-limiting toxicity and maximum tolerated dose for sunitinib. Studies have also been designed to determine a safe and effective treatment schedule for repeated dosing. On all treatment schedules, patients without evidence of unacceptable toxicity or disease progression after the first cycle of treatment were permitted to receive continuing cycles of treatment until they experienced unacceptable toxicity or disease progression.

1.3.5 Pharmacokinetics

The results of both single-dose and multiple-dose studies have demonstrated the favorable pharmacokinetic properties of sunitinib [25]. The Cmax and AUC appear to have increased in a proportional manner with an increase in dose after single doses of 50 to 350 mg as well as after multiple doses of 25 to 100 mg. The elimination half-life of sunitinib and its active metabolite, SU012662, are approximately 40 hours and 80 hours, respectively. Consistent with the linear pharmacokinetics of sunitinib and its active metabolite SU012662, their steady state dose-corrected plasma exposures were similar between 4/2 schedule and continuous daily dosage (CDD) schedule. The time to achievement of steady state with daily dosing of sunitinib has been assessed using trough concentrations of sunitinib, SU012662, and total drug measured during multiple dosing. These data indicate that steady-state conditions were achieved by approximately Day 10 to 14 for sunitinib. For SU012662 and total drug, steady-state conditions were achieved by Day 14 and Day 10, respectively. These findings are consistent with the half-life of sunitinib and SU012662.

Sunitinib and SU012662 concentrations measured through 3 cycles of therapy have shown that the Cmax, AUC 0-24 hr, and trough plasma drug concentrations (Cmin) during Cycle 2 or Cycle 3 were not increased above those observed in Cycle 1. Therefore, increases in plasma drug concentration would not be expected during subsequent cycles of therapy. Food does not have a significant effect on the bioavailability of sunitinib, and thus sunitinib may be administered without regard to meals. Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, producing the active metabolite, SU012662 which is also metabolized by CYP3A4. No other major metabolite has been identified. Accumulation with multiple doses of sunitinib has been noted but is consistent with the prolonged half-lives of sunitinib (~40 hours) and its active metabolite, SU012662 (~80 hours). Chronic accumulation has not been observed across dosing intervals.

1.3.6 Clinical Safety

The primary DLT in the phase 1 studies appeared to be fatigue/asthenia, which generally occurred 10 to 15 days after start of therapy, and was readily reversible upon discontinuation of sunitinib malate treatment. Fatigue appeared to increase in frequency with an increase in drug exposure. The maximum tolerated dose has been defined as 50 mg in phase 1 clinical studies in subjects with advanced solid tumors, subjects with AML, and subjects with imatinib mesylate-resistant GIST.

The most serious treatment-related adverse events associated with sunitinib malate treatment of solid tumor subjects were pulmonary embolism (1.1%), thrombocytopenia (1.1%), tumor hemorrhage (0.9%), febrile neutropenia (0.4%), and hypertension (0.4%). The most common treatment-related adverse events (experienced by at least 20% of the subjects) of any grade included fatigue (48.7%); gastrointestinal disorders, such as diarrhea (39.1%), nausea (35.6%), stomatitis (27.1%), dyspepsia (24.0%), and vomiting (22.2%); skin discoloration (29.3%); dysgeusia (27.8%); and anorexia (21.6%). The maximum severity of any of these adverse events was assessed as Grade 3. Fatigue (8.2%), hypertension (5.8%) and neutropenia (5.8%) were the most common treatment-related adverse events of Grade 3 maximum severity and lipase increase (1.8%) was the most frequently occurring treatment-related adverse event of Grade 4 maximum severity in subjects with solid tumors. The degree of adverse event severity appears to correlate with higher drug exposure and/or lower subject performance status. Most patients who experienced dose limiting toxicities (DLTs) in phase I studies were noted to have combined trough plasma concentrations of sunitinib and SU012662, ≥100 ng/ml [26].

Decreases in left ventricular ejection fraction (LVEF) of ≥ 20% and to below the lower limit of normal occurred in subjects receiving both sunitinib malate and placebo. The LVEF declines do not appear to have a cumulative effect with repeated dosing or permanent effect since they often improved with temporary discontinuation of treatment and may not recur with reintroduction of sunitinib malate. At doses higher than the recommended human dose (RHD), sunitinib has the potential to inhibit the cardiac action potential repolarization process (e.g. prolongation of QT interval). The clinical relevance of these findings is unknown as no clinically significant QTc prolongation has been observed in completed clinical studies.

1.3.7 Efficacy Results

Two phase II trials of sunitinib in cytokine-refractory, metastatic RCC have been conducted [27, 28]. Both trials enrolled cytokine-refractory, metastatic RCC patients with measurable disease. Sunitinib was administered as 50 mg daily for the first 4 weeks of repeated 6-week cycles. The first trial included all histologic subtypes and demonstrated an objective partial response in 25 of 63 total patients (objective response rate 40%). The second trial restricted eligibility to clear cell RCC and required both prior nephrectomy and RECIST-defined progression after prior cytokine therapy. This trial of 106 patients reported 1 complete and 40 partial responses (objective response rate 39%, much higher than previously reported for conventional cytokine based therapy for metastatic RCC).

The success seen in the phase II trials led to a subsequent phase III trial comparing sunitinib (50 mg daily for four weeks, followed by two weeks off) to interferon-alpha (INFa) (9 million units three times per week) in previously untreated patients with metastatic clear cell RCC [6]. Overall, a significantly better objective response rate (39% vs. 8%) and median progression-free survival (11 months vs. 5 months, hazard ratio 0.54) were determined. The final analysis of the trial showed that overall survival (OS) was prolonged with sunitinib (median 26.4 versus 21.8 months, hazard ratio 0.82, 95% CI 0.67-1.00, p=0.051) [29] although the OS analysis was complicated as almost half the patients were given a VEGF inhibitor post progression (either as treatment after progressing on IFNa or as a second-line therapy after progression on sunitinib). Regardless, subsequent multivariate analysis of survival showed that initial treatment with sunitinib was a statistically significant predictor of prolonged survival, further demonstrating its efficacy in the first line setting.

1.4 Rationale

Alternate schedules: While early preclinical studies intended to administer a continuous dose of sunitinib, eventually, the current 4 weeks on followed by 2 weeks off (schedule 4/2) was chosen for clinical drug development to allow for recovery from bone marrow and adrenal toxicities that were observed in animal models [26]. Thus, the standard schedule (SS) of sunitinib (50 mg once a day for four weeks followed by a 2 week treatment break; 4/2) was tested in phase I studies and demonstrated clinical efficacy with acceptable toxicities.

In clinical practice, it is often noted that adverse effects increase throughout each cycle, and tend to be worst in the final two weeks of the treatment cycle. Alternative schedules of sunitinib have been explored in clinical studies with the goal of improving drug tolerance and delivered dose intensity. A recent phase II study comparing a 37.5 mg continuous daily dose (CDD) regimen to schedule 4/2 demonstrated no differences in drug tolerance or patient reported symptoms, but established superiority of schedule 4/2 over CDD in time to tumor progression [18]. These data support the notion that higher intermittent dosing is clinically superior to lower dose, continuous administration.

An alternative dosing schema that has been used is 2 weeks on / 1 week off (schedule 2/1), in an effort to decrease adverse effects while continuing treatment. The Cleveland Clinic experience of 30 patients on the 2/1 schedule has revealed a significant improvement in drug tolerance, with no grade 4 toxicities observed on the 2/1 schedule, with less than 30% of patients experiencing grade 3 toxicity [30]. In addition, 73% of patients' worst toxicity on the 2/1 schedule was less severe than on the 4/2 schedule, and no patient's worst toxicity on the 2/1 schedule was greater than that on the 4/2 schedule (p<.0001). Fatigue and hand-foot syndrome, two of the most common toxicities, were significantly less severe on the 2/1 schedule than on the 4/2 schedule (p<.0003 in both cases). Median overall treatment duration of these patients initially on the 4/2 and, subsequently on the 2/1 schedule was 12.6 months and 11.9 months respectively. Median progression free survival (PFS) was approximately 12.7 months. These data suggest that patients with dose limiting toxicities on the 4/2 schedule are able to continue sunitinib treatment on a 2/1 schedule.

Neri et al. prospectively evaluated maintenance of dose intensity and drug tolerance in 31 patients treated with schedule 2/1, 10 of whom had previously been on the standard schedule (SS). The incidence of ≥ grade 3 fatigue and HFS in this study were 16.1% and 0% respectively [31]. Table 1 depicts a comparison of reported toxicities from schedule 4/2 reported in clinical trials of sunitinib.

MD Anderson Cancer Center evaluated one hundred eighty five patients treated with frontline sunitinib for clinical outcome and toxicity as a function of treatment schedule. Eighty- seven percent started out receiving sunitinib on a conventional 4/2 schedule. During treatment, 53% of patients continued on a conventional treatment schedule and 47% initiated or transitioned to an alternate schedule, which mainly consisted of treatment with sunitinib two weeks on and one week off. Baseline characteristics were similar. Adverse effects prompting schedule modification included fatigue (64%), hand-foot syndrome (38%) and diarrhea (32%). Median time to schedule change was 5.6 months. Median overall survival (OS) was 17.7 months (95% CI = 10.8 to 22.2 months) on conventional schedule compared to 33.0 months (95% CI = 29.3 to not estimable) on an alternate schedule ($P < 0.0001$). By multivariable analysis; poor ECOG PS, increased LDH, decreased albumin, unfavorable Heng criteria, and conventional schedule were associated with decreased OS ($P < 0.05$). [32, and unpublished data]. Comparison of toxicity prevalence before and after schedule adjustment demonstrated a clear reduction in toxicity rates Table 2.

Moreover, dynamic microbubble ultrasounds (DCE-US) in patients receiving sunitinib has demonstrated reduction of tumor blood volume at day 7 and day 14, compared to baseline, with no further reduction in blood flow from day 14-28 [33]. These findings suggest that the putative anti-tumor mechanism of sunitinib, i.e. reduction in tumor-associated blood flow, is optimized after 14 days, and dosing of sunitinib from day 15-28 may increase toxicity without meaningfully contributing to efficacy. Taken together, these data provide further impetus to explore modified schedules of sunitinib. **We hypothesize that sunitinib administered on a 2/1 schedule leads to a reduced incidence of ≥ grade 3 fatigue, hand-foot syndrome and diarrhea when compared to historical data, while maintaining clinical efficacy**.

Table 1: Comparison of the incidence of selective toxicities of VEGFR inhibitors in metastatic renal cell carcinoma

		Fatigue		**HFS**		**Diarrhea**		**Low Platelets**	
	No. of patients	All grade	Grade 3+	All grade	Grade 3+	All grade	Grade 3+	All grade	Grade 3+
Sunitinib									
Phase III vs. IFN[6]	375	54%	11%	29%	9%	61%	9%	68%	9%
EFFECT[18]	146	65%	9%	32%	10%	59%	6%	75%	13%
COMPARZ[20]	548	63%	7%	50%	12%	57%	8%	34%	16%
CCF 2/1[30]	30	54%	7%	17%	0%	36%	3%	7%	0%
MDACC*	-	62%	-	32%	-	32%	-	3%	-

before modification									
MDACC* after modification	-	19%	-	2%	-	2%	-	0%	-
Pazopanib									
Phase III[35]	290	19%	2%	<10%	<1%	52%	4%	32%	1%
COMPARZ[20]	554	55%	11%	29%	6%	63%	9%	10%	3%
Tivozanib									
Phase III[36]	259	19%	3%	13%	2%	18%	2%	17%	1%

*unpublished data

Table 2: Prevalence of toxicity before and after schedule modification (MD Anderson Cancer Center data)

Adverse Event	Before schedule modification N = (%)	At first follow up after schedule modification N = (%)
Fatigue	40 (64)	18 (29)
Hand foot syndrome	24 (38)	6 (10)
Diarrhea	20 (32)	4 (6)
Mucositis	14 (22)	3 (5)
Nausea/vomiting	9 (14)	7 (11)
Dysgeusia	6 (10)	0
Rash	6 (10)	0
Hypertension	6 (10)	3 (5)
Anorexia	5 (8)	1 (1.5)
Mouth sores	3 (5)	0
Laboratory Abnormalities		
ANC < 1K/uL	3 (5)	1 (1.5)
Platelet count < 100 K/uL	2 (3)	1 (1.5)
TSH level > 4.20 IU/mL	2 (3)	0

2.0 OBJECTIVES

2.1 Primary Objective

To assess the incidence of ≥ grade 3 treatment-related fatigue, hand-foot syndrome and/or diarrhea in metastatic renal cell carcinoma (mRCC) patients receiving sunitinib on a 2 weeks on / 1 week off schedule (schedule 2/1).

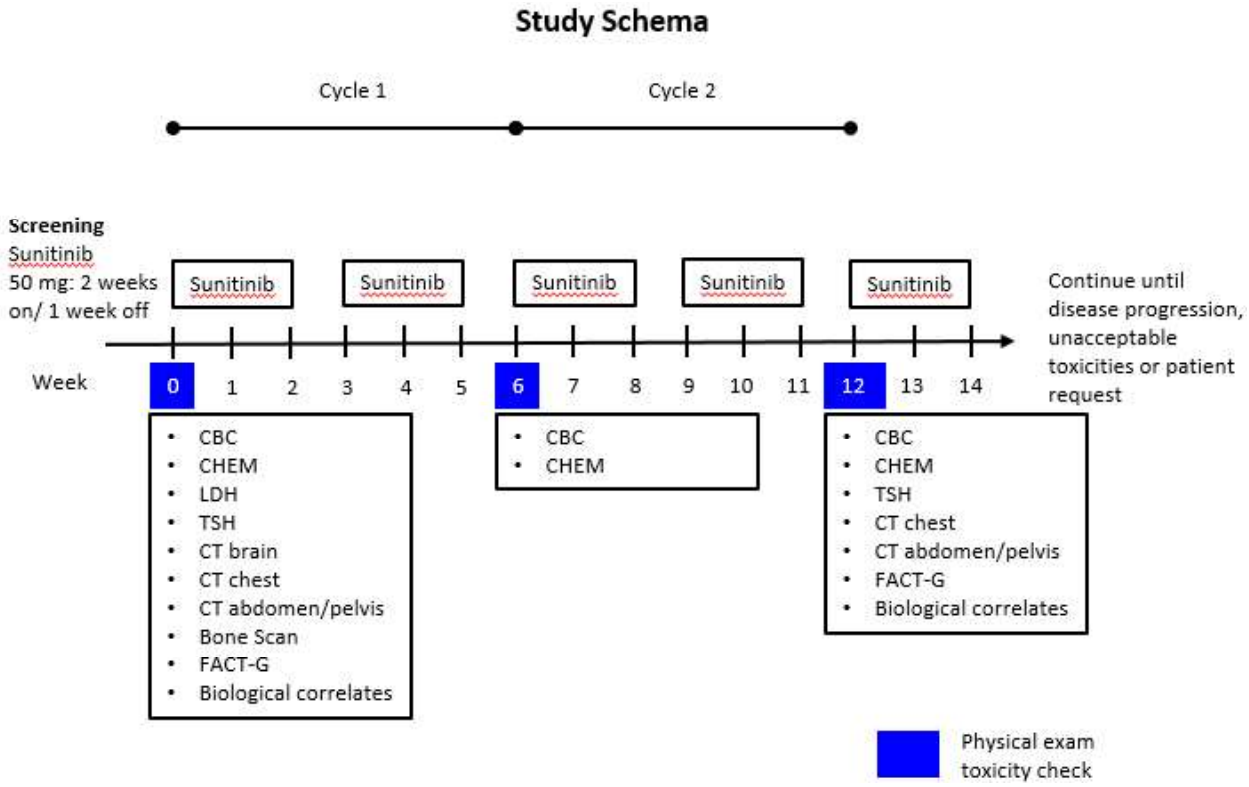
2.2 Secondary Objective(s)

- To assess the progression-free survival (PFS) of schedule 2/1 in patients with metastatic RCC.
- To assess the incidence of all ≥ grade 3 toxicities on schedule 2/1
- To assess the incidence of dose reductions, dose interruptions, dose delays and rate of discontinuation for toxicity in patients with mRCC receiving sunitinib schedule 2/1.
- To assess patient reported outcomes
- To assess biologic correlatives by measuring circulating DNA levels
- To assess correlation of tumor associated macrophages with response to therapy

3.0 STUDY DESIGN

3.1 Study schema

This is a single arm phase II study of sunitinib administered to treatment-naïve patients with clear cell mRCC. Patients will be treated with sunitinib at a starting dose of 50mg 2/1 with schedule/dose modifications for toxicity and treated until RECIST-defined progressive disease or unacceptable toxicity. Adverse events will be graded and categorized using CTCAE version 4.03 criteria. Staging studies will be assessed per RECIST v 1.



Sunitinib starting dose 50 mg by mouth daily given for 2 weeks "on" followed by 1 week "off"
1 cycle=6 weeks

3.2 Study Calendar

	Screening[a]	C1D1 (week 1)	Odd Cycles, D42 (up to Cycle 11)	Even Cycles, D42 (up to Cycle 12)	Cycles Beyond C12[h]	End of Treatment	End of study
Informed consent	X						
History, physical exam and weight	X	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X
Toxicity assessment[b] and concomitant medications	X	X	X	X	X	X	X
CBC differential, platelet[c]	X	X[c]	X	X	X	X	X
Serum chemistry[c]	X	X[c]	X	X	X	X	X
TSH[d]	X			X	X	X	
LDH	X						
B-HCG for women of child-bearing age	X						
CT or MRI brain[e]	X						
CT chest/ abdomen/pelvis[f] (with contrast)	X			X	X		X[i]
Bone scan[e]	X						
FACT-G QOL[g]		X		X			
Serum, plasma & buffy coat samples for biological correlates[j]		X		X	X	X	

One Cycle= 42 days (6 weeks).
For each visit, the following variations in time are acceptable:
A window of ± 5 days is allowed for labs and follow-up visits (except C1D1); ±7 days is allowed for restaging scans.
Patients are to record blood pressure measurements in BP log daily for the first week and at least once per week thereafter. Daily intake of sunitinib should be recorded in the pill diary throughout treatment. Both will be collected during office visits by provider.

[a]Screening studies must be completed within 28 days prior to administration of protocol therapy. Height to be collected at screening.
[b]Vital signs to include temperature, blood pressure and pulse
Toxicity assessment using CTCAE v 4.03
[C] CBC, to be performed with differential and platelet count; Serum Chemistry to include albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. **CBC/chemistry does not need to be repeated at C1D1 if previous test was within last 14 days**
[d]Thyroid function studies (TSH) should be performed every other cycle or more frequently if clinically indicated
[e]Bone scan and CT brain should be performed during screening. Subsequently, repeat scans to be performed only if clinically indicated. MRI brain in lieu of CT brain acceptable.
[f] CT chest/abdomen/pelvis to be repeated every 2 cycles
[g]FACT-G to be administered at visits during baseline, week 12, week 24 and week 36 assessments prior to MD encounter. Study team to check for completion of QOL data: more than 50% questions in each subscale, and at least 80% of questions overall in each questionnaire should be answered for the questionnaire to be considered complete.

[h] Labs and follow-up visits can be every 12 weeks after completion of 12 cycles, at the discretion of the treating physician
[i] EOS visit does not require CT scans if performed within the preceding 12 weeks.
[j] Biological correlates to include characterization of circulating DNA and tumor associated macrophages.

4.0 PATIENT SELECTION

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for enrollment:

1. Histologically or cytologically-confirmed metastatic renal cell carcinoma of clear cell histology. Prior nephrectomy is not a requirement for eligibility
2. Age ≥18 years
3. Measurable or evaluable metastatic disease per RECIST v 1
4. ECOG performance status 0-1
5. Normal organ and bone marrow function as defined by:
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 x laboratory upper limit of normal (ULN)
    - Total serum bilirubin ≤ 2.0 x ULN
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Platelets ≥ 100,000/μL
    - Hemoglobin ≥ 9.0 g/dL (transfusion permitted)
    - Serum calcium ≤ 12.0 mg/dL
    - Serum creatinine ≤ 2.5 mg/dL
6. Patients with a history of deep venous thromboembolism or pulmonary embolism on treatment with anticoagulation are eligible for the study.
7. Subjects must have the ability to understand and the willingness to sign a written informed consent document

4.2 Exclusion Criteria

The presence of any of the following will exclude a patient from study enrollment.

1. Prior treatment with sunitinib or any other systemic therapy in the metastatic setting (prior neo/adjuvant therapy will be allowed if completed > 6 months prior to registration and therapy not discontinued for toxicity)
2. Uncontrolled hypertension (defined as blood pressure >140/90 mm Hg not controlled with anti-hypertensives)
3. Prior intraabdominal, intrathoracic, vascular, spinal or intracranial surgery or radiation therapy within 4 weeks of starting treatment
4. History of or known brain metastases, spinal cord compression, or carcinomatous meningitis
5. New York Heart Association (NYHA) grade II or greater congestive heart failure
6. Current treatment on another therapeutic clinical trial

7. Any of the following within the preceding 6 months- myocardial infarction, severe/unstable angina, severe peripheral vascular disease (claudication) or procedure on peripheral vasculature, coronary/peripheral artery bypass, graft, cerebrovascular accident or transient ischemic attack, clinically significant bleeding
8. Pregnant or breastfeeding women are excluded from this study because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with sunitinib. Breastfeeding must be discontinued if the mother is treated with sunitinib
9. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness
10. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with sunitinib. In addition, these patients are at increased risk of lethal infections when treated with marrow suppressive therapy

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

5.0 REGISTRATION

All patients will be registered in the approved Office of Research Administration (ORA) database at MD Anderson. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded. For registration procedures for this protocol, please refer to Section 15.2 of the protocol and the Multicenter Management Plan (Appendix D).

6.0 TREATMENT PLAN

6.1 Sunitinib Administration

Treatment will be administered on an outpatient basis. Sunitinib will be initially dosed at 50 mg by mouth daily (QD) for 2 weeks followed by a one week break. Cycles of treatment will be defined as 6 week intervals regardless of dosing interruptions. Thus patients will receive sunitinib during weeks 1, 2, 4 and 5 of each 6 week (42-day) cycle, with treatment breaks during weeks 3 and 6. Sunitinib will be given without regard to meals. **Patients will record blood pressure measurements daily for the first week and at least once weekly thereafter throughout the course of treatment using blood pressure logs that will be provided to them [Appendix 2].**

Patients who experience toxicity per Section 8 may undergo dose/schedule modification as indicated per section 7. Reported adverse events and potential risks of sunitinib are described in Section 8.0. Appropriate dose and schedule modifications for sunitinib are described in Section 7.0.

No investigational or commercial agents or therapies other than sunitinib may be administered with the intent to treat the patient's malignancy. **The patient will be provided a**

Patient Pill Diary [Appendix 1] and instructed regarding its use to record each dose of oral medication.

6.2 General Concomitant Medications and Supportive Care Guidelines

Patients may receive Epogen/Procrit/Aranesp for anemia and a bisphosphonate for hypercalcemia and/or bone metastases as required. Anti-emetic therapy of any kind is permitted. Full transfusional support is permitted. The prophylactic use of growth factors is not allowed. The use of pyridoxine (vitamin B6) for the treatment of hand-foot syndrome is permitted. Palliative radiotherapy is allowed as long as there is no progressive disease per RECIST criteria; sunitinib may or may not be held during radiotherapy at the discretion of the treating physician. If held, dose changes must be recorded. No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biological response modifiers, hormone therapy or immunotherapy. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Sunitinib is metabolized primarily by liver enzymes, in particular CYP3A4. Agents known to induce CYP3A4 including dexamethasone should be avoided. Agents known to inhibit this enzyme (e.g., grapefruit juice) should also be avoided. In particular, ketoconazole should be avoided if possible, since a clinical interaction study of sunitinib indicated that up to a 2-fold increase in plasma levels of sunitinib was induced by ketoconazole. In addition, concomitant treatment with the following drugs with dysrhythmic potential (ie, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended.

6.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue indefinitely until one of the following criteria applies:

- Disease progression per RECIST version 1.
- The investigator considers it, for safety reasons, to be in the best interest of the patient.
- Unacceptable adverse event(s) related to treatment, defined as a grade 3 or 4 toxicity (per CTCAE v 4.03) that fails to recover to < Grade 2 in the absence of treatment within 4 weeks
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient decision to withdraw from treatment (partial consent) or from the study (full consent)
- Pregnancy during the course of the study for a child-bearing participant

The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

If in the opinion of the investigator, the patient demonstrates disease progression by RECIST, but the patient is demonstrating obvious clinical benefit to sunitinib therapy, the investigator may choose to continue patient on study. At the time that clinical benefit from study drug is no longer apparent, investigator will take patient off study and off study drug.

6.4 Duration of Follow Up

Patients will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

7.0 DOSING DELAYS / DOSE MODIFICATIONS

Table 3: Dose/Schedule Levels

Table 3a defines treatment levels of sunitinib with dose and schedule specifications. The starting dose for all patients will be 50 mg on a 2/1 schedule. Dosing schedule may be changed to 50 mg 1 week on followed by 3 days off alternating with 1 week on and 4 days off and repeated for a 6-week cycle at outlined in table 3a for toxicities described in table 3b. Patient requiring further reduction in treatment level will be dose reduced to 37.5 mg on a 2/1 schedule, and so on per table 3a. Intra-patient re-escalation back to the previous treatment level is permitted in the absence of grade ≥ 3 hematologic or grade ≥2 non-hematologic treatment-related toxicity in the previous cycle. Table 3b outlines indications for withholding treatment and for reductions in treatment levels.

Treatment Level	Sunitinib dose	Schedule
Level 0 (starting dose)	50 mg	2 weeks on/ 1 week off
Level -1	50 mg	1 week on/ 3 days off alternating with 1 week on/4 days off
Level -2	37.5 mg	2 weeks on/ 1 week off
Level -3	37.5 mg	1 week on/ 3 days off alternating with 1 week on/4 days off
Level -4	25 mg	2 weeks on/ 1 week off
Level -5	25 mg	1 week on/ 3 days off alternating with 1 week on/4 days off

Table 3a: Treatment levels of sunitinib with dose and schedule specifications

Table 3b: Indications for withholding treatment and reductions in treatment levels

Grade	Type	Management/Next Dose for Sunitinib
≤ Grade 1[+]	Any except vascular [+]	No change in treatment level
Grade 2	Hematologic	Continue at same treatment level
	Cardiac	Continue at same treatment level except in the event of: -Decrease of LVEF by an absolute value of 20% and to below the lower limit of normal -Non-urgent ventricular paroxysmal dysrhythmia requiring intervention. In these cases: withhold dose until toxicity is grade ≤1, then reduce the treatment by 1 level and resume treatment. **If the patient was on level 0, then need to resume at level -2**
	Non-cardiac and non-hematologic	Continue at same dose level
Grade 3	Hematologic***	Withhold dose until ANC>1,000 and Platelets > 50,000, then resume treatment at the same level or reduce by 1 level at the discretion of the investigator.
	Cardiac	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then resume treatment at the same level or reduce the dose by 1 level at the discretion of the investigator.**
	Non-cardiac and non-hematologic*	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then resume treatment at the same level or reduce by 1 level at the discretion of the investigator.
Grade 4	Hematologic***	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce by 1 level and resume treatment**.
	Cardiac	Remove from protocol.
	Non-cardiac and non-hematologic	Withhold dose until toxicity is grade ≤1 or has returned to baseline, then reduce by 1 level and resume treatment, or discontinue at the discretion of the investigator.

[+]Except vascular- for all vascular toxicities, including grade 1, drug must be held and appropriate treatment initiated. Sunitinib may be restarted at the discretion of the treating MD.

* Patients with grade 3 asymptomatic biochemistry laboratory abnormalities may continue treatment at the same dose level without interruption at the discretion of the investigator.
** Hypertension may be managed appropriately with anti-hypertensives, and the patient may continue sunitinib provided the blood pressure is controlled to < 160/90 mmHg within 4 weeks. Patients who are unable to have blood pressure controlled to < 160/90 mmHg within 4 weeks should be removed from the study. **Patients with congestive heart failure must be removed from study.**
***Patients who develop grade 3 or 4 lymphopenia may continue study treatment without interruption.

All intra-patient dose reductions are relative to the lowest dose level of the current cycle. If the current treatment level is -5 and the toxicity guidelines above indicate a further treatment/dose reduction is necessary, treatment should be discontinued. Patients are to be removed from study if toxicity does not resolve to grade 1 or less within

4 weeks off study drug.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

8.1 Adverse Events and Potential Risks

8.1.1 Adverse events and potential risks list

Adverse events will be assessed and will be graded according to the NCI CTCAE v4.03.
CTCAE v4.3 can be accessed on the internet at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
All toxicities ≥ Grade 4, unexpected AND drug related should be reported (using a MedWatch form) to the Principal Investigator, the Data Safety and Toxicity Committee and the IRB.

To date, over 1500 subjects with advanced malignancies have been treated with sunitinib malate. Multiple phase 1, 2 and 3 studies have been conducted or are underway. Study subjects enrolled on the initial clinical studies received sunitinib malate in a free-base formulation, but study subjects enrolled on protocols activated after February 2002 were treated with the sunitinib malate salt formulation. A prior study demonstrated the bioequivalence of these 2 formulations.

The primary DLT in the phase 1 studies appeared to be fatigue/asthenia, which generally occurred 10 to 15 days after start of therapy, and was readily reversible upon discontinuation of sunitinib malate treatment. Fatigue appeared to increase in frequency with an increase in drug exposure. DLT experienced during the first cycle of therapy was observed more frequently in subjects on Schedule 4/2 than in subjects on Schedule 2/2. Overall, the most frequent adverse events associated with sunitinib malate treatment of greatest severity have been constitutional (fatigue/asthenia), gastrointestinal (nausea, vomiting, diarrhea), and hematologic (neutropenia, thrombocytopenia). The degree of adverse event severity appears to correlate with higher drug exposure and/or lower subject performance status. A similar pattern was observed for subjects with previous chemotherapy in comparison to chemotherapy-naïve subjects.

In studies evaluating starting doses that ranged from 75 to 100 mg daily, cardiac hypokinesis and clinical signs of congestive heart failure were reported in 4 of 62 advanced acute myeloid leukemia subjects; however, the causal relationship to sunitinib malate was confounded by disease morbidities and prior anthracycline exposure. At the 50-mg dose level, asymptomatic

decreases in cardiac ejection fraction were observed in <5% of solid tumor subjects, either with or without a prior history of cardiovascular disease or anthracycline exposure. Decrease in LVEF by MUGA is reversible and does not appear to have cumulative effect with repeat drug exposure. A review of cardiac and other safety data from clinical and preclinical studies is provided in the Investigator Brochure.

The maximum tolerated dose has been defined as 50 mg in phase 1 clinical studies in subjects with advanced solid tumors, subjects with AML, and subjects with imatinib mesylate-resistant GIST. Subjects receiving this dose of sunitinib malate achieved target plasma concentrations of sunitinib malate plus SU012662 in the range of 50 to 100 ng/mL.

8.2 Definitions

8.2.1 Adverse Events

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

External adverse events are adverse events experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the Institutional Review Board has jurisdiction.

Internal adverse events are adverse events experienced by subjects enrolled at the site(s) under the IRB's jurisdiction for either multicenter or single-center research projects.

The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

8.2.2 Serious Adverse Events

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

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- 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.

8.2.3 Expectedness

Adverse Events can be Expected or Unexpected.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

8.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.
- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of AEs throughout the subject's participation in the study, beginning at the time of initiation of treatment. Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject which occur after the subject has initiated treatment are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study), requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event.

The investigator will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting, available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with initiation of treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the MD Anderson Cancer Center Principal Investigator.

Investigative sites will report serious adverse events to their respective IRB according to the local IRB's policies and procedures in reporting serious adverse events.

8.4.1 Pfizer Reporting

The Investigator Initiated Research Serious Adverse Event Form provided by Pfizer will be utilized for reporting all SAEs to Pfizer.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.0.

Sunitinib

Chemical Name: 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid(2-diethylamino-ethyl)-amide; compound with (S)-2-hydroxy-succinic acid.

Other Names: SUNITINIB L-Malate salt; SU010398; PHA-290940AD; Sutent; SUNITINIB, sunitinib malate

Classification: Receptor tyrosine kinase inhibitor (RTK)

Molecular Formula: $C_{22}H_{27}FN_4O_2.C_4H_6O_5$

Mode of Action: Sunitinib malate is a receptor tyrosine kinase inhibitor involved in tumor proliferation and angiogenesis, specifically inhibiting platelet derived growth factor receptor, vascular endothelial growth factor receptor, stem cell factor receptor, Fms-like tyrosine kinase-3 receptor, and ret proto-oncogene.

Metabolism: Cytochrome P450 (CYP) 3A-mediated N-deethylation to form SU012662 was the major pathway of the metabolism of sunitinib in liver microsomes from rats, monkeys, and humans. Sunitinib metabolism was predominately mediated by CYP3A4 and produced an active metabolite, SU012662. This metabolite and sunitinib were the only major drug-related compounds found in systemic circulation in mice, rats, monkeys, and humans. Minor metabolites of sunitinib were mainly found in excreta and were either not found or found at very low levels in plasma. Sunitinib and SU012662 were not potent inducers or inhibitors of major CYP450 enzymes. The efflux transporters, P-gp and BCRP, did

not appear to play a significant role in the pharmacokinetics of sunitinib. Therefore, sunitinib and SU012662 are predicted to have a low potential to cause clinically relevant drug-drug interactions mediated by CYP450 enzymes and the efflux transporters. However, concomitantly administered CYP3A4 inducers and inhibitors may affect the pharmacokinetics of sunitinib.

Product description:

Physical description: Yellow to orange powder

Molecular weight: 532.57 Daltons

Drug procurement: Sunitinib will be supplied by Pfizer will be used for this study. Sunitinib malate is distributed by Pfizer as 12.5 mg, 25 mg, and 50 mg capsules with mannitol, croscarmellose sodium, povidone, and magnesium stearate. Each opaque plastic bottle contains 30 capsules

Storage requirements*:* Store at controlled room temperature (150 to 300 C), and protect from light.

Stability: The shelf life for the 12.5 mg capsule is 24 month. The shelf life for the 25 mg and 50 mg capsules is 36 months.

Route of administration*:* Oral. Sunitinib malate may be administered without regard to meals.

Drug Accountability: The investigator or designated study personnel are responsible for maintaining accurate dispensing records of the study drug. All study drugs must be accounted for, including study drug accidentally or deliberately destroyed. Under no circumstances will the investigator allow the investigational drug to be used other than as directed by the protocol. If appropriate, drug storage, drug dispensing, and drug accountability may be delegated to the pharmacy section of the investigative site.

Drug Destruction*:* At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on a drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

Patient Care Implications: A yellow discoloration of the skin area may result following direct contact with the capsules. Wash the exposed area with soap and water immediately.

Potential Drug Interaction: Sunitinib malate is metabolized primarily by liver enzymes, particularly CYP3A4. CYP3A4 inducers (e.g., rifampin, dexamethasone) and CYP3A4 inhibitors (e.g., grapefruit juice, ketoconazole) should be avoided, if possible. Rifampin lowers sunitinib

malate Cmax concentration by more than 2-fold. Ketoconazole increases sunitinib malate Cmax by 1.6 fold. Dose reduction with the CYP3A4 inhibitors is recommended, based on clinical symptoms. Concomitant treatment with dysrhythmic drugs, i.e., terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide, is not recommended.

10.0 PATIENT REPORTED OUTCOMES (PROs – See Appendix #3)

10.1 Quality of life (QOL) questionnaires

QOL questionnaires will be utilized to evaluate patient reported outcomes. This would include the Functional Assessment of Cancer Therapy- General (FACT-G) scale.

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System is a collection of health-related quality of life (HRQOL) questionnaires targeted to the management of chronic illness [34]. The validated FACT-G scale is a 27-item compilation of general questions divided into four primary QOL domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. It is appropriate for use with patients with any form of cancer is widely used for assessing health-related QOL for different cancers. This questionnaire was designed for self-administration, written at 4th grade reading levels, and can be completed in 5-10 minutes [34]. A higher total score suggests well-being, and a lower score is an indication of inferior QOL.

10.2 Rationale

With the availability of several new targeted agents that prolong survival in mRCC, there is increasing emphasis on patient preferences based on treatment related quality of life. Two recent randomized trials, COMPARZ and PISCES (pending publication), demonstrated differences in QOL amongst sunitinib and its active comparator, pazopanib [19, 20]. The impact of treatment related toxicities on patients' QOL while receiving sunitinib on the 2/1 schedule is thus an important end-point of interest.

10.3 Data collection

QOL questionnaires will be administered at the initiation of treatment (**baseline**), and then at **week 12, week 24 and week 36**. **These will be administered by the study team prior to patient encounters with the physician**. The study team will also check for completion of all elements in each questionnaire, which will be collected from the patient at the end of that encounter. Only forms with more than 50% answers in each subscale will be considered acceptable. Moreover, at least 80% of questions overall in each questionnaire should be answered in order for it to be considered acceptable for analysis.

Missing data: Prorating subscale scores is acceptable as long as **more than 50%** of the items have been answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total (FACT-G) score is considered appropriate to score as long as **overall item response rate is greater than 80%** (e.g., at least 22 of 27 FACT-G items complete) [34].

10.4 Data analyses

The end-point for all three PROs would be the mean score at each time point**- baseline, week 12, week 24 and week 36.** Descriptive summary statistics will be calculated for all continuous variables (means, standard deviations, medians, ranges, percentage of patients scoring in the highest category for each item) for the items in the subscales each time point. The mean trajectories of each group over time will be plotted for the total scores, along with scores for physical well-being, social well-being, emotional well-being and functional well-being-specific scales for FACT-G.

11.0 CORRELATIVE STUDIES

11.1 Circulating Tumor DNA

Cell-free circulating tumor DNA may provide prognostic and pharmacodynamic information in patients treated with anticancer therapy. The advent of sensitive, high throughput sequencing has permitted the efficient investigation of tumor specific polymorphisms. In collaboration with Dr. Raghu Kalluri, we will assess patient serum for presence of circulating tumor DNA and perform exome sequencing to determine whether tumor specific DNA polymorphisms can be detected. Samples will be collected at baseline and defined restaging intervals to determine whether pretreatment levels correlate to outcome and whether treatment with and response to antiangiogenic therapy impacts levels of circulating tumor DNA.

11.2 Tumor Associated Macrophages

Emerging data suggest that bone marrow derived cells residing in the tumor microenvironment may modulate response to antiangiogenic therapy. Baseline infiltration of discrete populations of microenvironment modulating cells can be measured by co-staining archival tumor tissue with appropriate antibodies. These populations include tumor-associated macrophages (TAM), myeloid derived suppressor cells (MDSC) and t-regulatory cells. Quantitation of these cells and comparing them to clinical outcome will shed light on which of these cell populations is predictive for response to sunitinib therapy.

12.0 STUDY PARAMETERS

12.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed $\leq$ 28 days prior to administration of protocol therapy.

- Informed consent
- Demographics
- Medical history
- Complete physical examination

- Height
- Weight
- Vital signs including: Blood pressure, pulse and temperature
- Concomitant medications assessment including prescription, over the counter and herbal medications
- ECOG Performance Status
- Baseline symptoms assessment
- Laboratory studies:
    - Complete Blood Count (CBC) with differential and platelets
    - Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium
    - LDH ,TSH
    - ß-HCG for women of childbearing potential
- CT scan of brain, chest, abdomen and pelvis (with contrast). **An MRI brain performed with contrast in lieu of CT brain is acceptable, if within the study timeframe.**
- Bone scan at baseline

12.2 Treatment Period

Treatment cycles are 6 weeks long. For each visit, the following variations in time are acceptable:
A visit window of ± 5 days is allowed for labs and follow-up visits.
A window of ±7 days is allowed for restaging scans.
Schedule changes due to Holidays or weather that result in study procedures outside these windows will not be considered a protocol deviation.

Cycle 1, Day 1

Cycle 1, Day 1 evaluations do not need to be repeated if conducted within **7** days prior to administration of protocol therapy.

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse, and temperature
- Concomitant medications assessment including all current medications
- ECOG Performance Status
- Baseline symptoms assessment
- **Laboratory Studies: (waive if performed within the last 14 days)**
  Complete Blood Count (CBC) with differential and platelets
  Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
- **Correlative Studies:** QOL questionnaires: FACT-G
  Biological correlates : Serum, plasma, buffy coat samples

Cycle 1, Day 42

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse and temperature
- Concomitant medications assessment including all current medications
- ECOG Performance Status
- Toxicity Assessment
- **Laboratory Studies:** A window of ± 5 days is allowed for labs
  Complete Blood Count (CBC) with differential and platelets
  Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

Cycle 2, Day 42

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse and temperature
- Concomitant medications assessment including all current medications
- ECOG Performance Status
- Toxicity Assessment
- **Laboratory Studies:**
  Complete Blood Count (CBC) with differential and platelets
  Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
- **Correlative Studies:**
  QOL questionnaires: FACT-G
  Biological correlates : Serum, plasma, buffy coat samples
- **Restaging scans:** CT scan of chest, abdomen and pelvis (with contrast)

Subsequent cycles – each visit at Day 42

- The assessment and evaluation in subsequent visits will include all the items enlisted in cycle 2 day 42, except:
- Restaging scans that will be performed every even numbered cycle (cycle 4, 6, etc.)
- QOL questionnaires will be assessed at baseline, week 12, week 24 and week 36 only.
- Biological correlate : Serum, plasma, buffy coat samples will be collected at at baseline, week 12, week 24, week 36, and at the time of disease progression.
- Bone scan will be repeated in patients with bone metastases at baseline or at the development of signs/symptoms consistent with bone metastases.
- CT/MRI brain will not need to be repeated unless a patient was to develop clinical symptoms that warrant brain imaging, in which case the decision to conduct CT versus MRI of the brain will be at the discretion of the treating physician.
- TSH will be checked in every even numbered cycle and additionally if clinically indicated.

- After 12 cycles, labs and follow-up visits may be allowed every 12 weeks instead of every 6 weeks if clinically indicated at the discretion of the treating physician.

End of Treatment Visit

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse and temperature
- Concomitant medications assessment including all current medications
- ECOG Performance Status
- Toxicity Assessment
- **Laboratory Studies:**
  Complete Blood Count (CBC) with differential and platelets
  Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

End of Study - 30 Day Follow-Up

- Physical Examination
- Weight
- Vital signs including: blood pressure, pulse and temperature
- Concomitant medications assessment including all current medications
- ECOG Performance Status
- Toxicity Assessment
- CT scan of chest, abdomen and pelvis (with contrast) not required if performed within the preceding 12 weeks
- **Laboratory Studies:**
  Complete Blood Count (CBC) with differential and platelets
  Serum Chemistries: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

13.0 MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 12 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

13.1.1 Definitions

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

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

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

13.1.2 Disease Parameters

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

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

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

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

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

Target lesions All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be

those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance, the next largest lesion which can be measured reproducible should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

13.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-holding techniques, if possible.

PET-CT should not be used as an imaging modality

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

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

Tumor markers not applicable

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

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

13.1.4 Response Criteria

13.1.4.1 Evaluation of Target lesions

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. **Note**: the appearance of one or more new lesions is

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

13.1.4.2 Evaluation of Non-Target lesions

Response	Evaluation of Non-Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). **Note:** If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/ Non-PD [Incomplete response/ Stable Disease (SD)]	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD)	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of 'non-target' lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.1.4.3 Evaluation of Best Overall Response

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

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

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

* See RECIST 1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

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

13.1.5 Duration of Response

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

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

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

13.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

14.0 MULTICENTER PROCEDURES

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

14.1 Principal Investigators

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

14.2 Centralized Patient Registration and Randomization

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

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

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

14.2.1 Eligibility Exceptions

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

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

Any Serious Adverse Event (SAE) will be reported to the MD Anderson GU Department within 24 hours of knowledge of the event. MD Anderson GU Department will in turn notify Pfizer. The participating institution will submit the SAE to its own IRB according to institutional policy

and must forward a copy of the report to MD Anderson within 5 calendar days. The MD Anderson GU department will submit participating site SAE reports to the MDACC IRB and Pfizer.

SAE notifications and reports will be submitted to:

Email a completed SAE Form to:

MD Anderson GU Department (notifications and reports)
Subject: 2013-0944 SAE Notification
Email: GU2013-0944@mdanderson.org

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

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

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol deviations, violations, and unanticipated problems. The Protocol Chair will also be responsible for ensuring that all protocol deviations, violations, and unanticipated problems are reported to the MD Anderson IRB per MD Anderson institutional guidelines.

Participating Institutions: Protocol deviations, violations, and unanticipated problems occurring at a participating institution will be submitted to that institution's own IRB. A copy of the participating institution's IRB deviations, violations, and unanticipated problems report will be forwarded to MD Anderson by facsimile or via email within 7 calendar days after the original submission.

14.4.1 Definitions

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

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

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

Unanticipated Problems: An incident, experience or outcome, that is unexpected, related or possibly related to participation in the research and suggests that the research places subjects or

others at a greater risk of harm (including physical, psychological, economic, or social harm) that was previously known or recognized. These incidents do not meet the definition of an adverse event. Unanticipated problems are not limited to study participants, and may also include others such as family members and research staff.

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

14.5 Research Team Teleconferences

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

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

15.0 DATA AND PROTOCOL MANAGEMENT

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

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

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

15.1 Schedule of Data Submission

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

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

16.0 STATISTICAL CONSIDERATIONS

16.1 Definition of primary outcome/endpoint:

Composite rate of toxicity defined as the percentage of patients who experience one or more of the following ≥grade 3 toxicities using CTCAE version 4.03 criteria that are possibly, probably, or definitely related to study therapy: fatigue, HFS or diarrhea.

16.2 Definition of secondary outcomes/endpoints:

- Progression-free survival (PFS) defined as the time from treatment initiation to disease progression using RECIST v 1 or death.
- Incidence of all ≥grade 3 toxicities per CTCAE version 4.03 criteria, defined as the percentage of patients who experience any grade 3 or greater toxicity that is possibly, probably, or definitely related to study therapy.
- Dose reductions, dose interruptions, dose delays will be recorded using pill diaries maintained by patients that will be reviewed and recorded at each visit. This outcome will be reported as the percentage of patients who underwent one or more dose reductions, dose interruptions and/or treatment delays. The number of patients who discontinue treatment due to unacceptable toxicities will be recorded, and reported as a percentage of the total number of enrolled patients.
- Changes in the patient reported outcomes in FACT-G (general) scale during treatment on schedule 2/1
- Changes in circulating DNA levels with antiangiogenic treatment
- Correlation of tumor associated macrophages (TAM) with response to therapy

16.3 Sample size justification:

The primary goal of the trial is to estimate the likelihood that with a 2 weeks on/1 week off schedule a patient will experience at least one of the most commonly reported and troublesome grade 3 or worse sunitinib-related toxicities – fatigue, hand-foot syndrome, and diarrhea. The primary endpoint is the percentage of patients who experience one or more of these adverse events. A total of 60 patients will be accrued in order to estimate the likelihood of toxicity using a 95% confidence interval that has a half-width of <10% (assuming the observed composite toxicity rate is approximately 10-15%). If the upper bound of the confidence interval is less than 25% this will be taken as an indication that the 2/1 schedule has a better toxicity profile than the standard 4/2 schedule since from earlier randomized studies approximately 25-30% of patients on the 4/2 schedule can be expected to have these toxicities

16.4 Analytic plan for primary objective:

Toxicities will be tabulated by type and grade. A point estimate and its 95% confidence interval of the primary endpoint will be calculated and presented based on a Bernoulli distribution.

16.5 Analytic plan for secondary objectives:

- PFS will be measured from the date of initiation of treatment to the first of documented progression or death; and will be estimated using the Kaplan-Meier method. PFS is expected to be comparable to that seen with 4/2 (11 month median); however if the upper bound of the interval is less than 8 months this will be taken as an indication that the efficacy of 2/1 is inferior to that of 4/2.

- Toxicities will be tabulated by type and grade, and the incidence of all ≥ grade 3 toxicities will be calculated by CTCAE v 4.03 along with a 95% confidence interval

- The percentage of patients who underwent one or more dose reductions, dose interruptions and/or treatment delays will be estimated along with a 95% confidence interval. The number of patients who discontinue treatment due to unacceptable toxicities will be recorded, and reported as a percentage of the total number of enrolled patients along with 95% confidence interval.

- Health-related quality of life (HRQOL) will be assessed by FACT-G questionnaires as a secondary endpoint. Questionnaires will be administered at baseline, week 12, week 24 and week 36. Descriptive summary statistics will be calculated for all continuous variables (means, standard deviations, medians, ranges, percentage of patients scoring in the highest category for each item) for the items in the subscales each time point. The mean trajectories of each group over time will be plotted for the total scores, along with scores for physical well-being, emotional well-being, functional well-being, and renal-specific scales for FACT-G.

17.0 REFERENCES

1. SEER Stat Fact Sheets: Kidney and Renal Pelvis. Accessed July 2013 http://seer.cancer.gov/statfacts/html/kidrp.html
2. Murai M, Oya M. Renal cell carcinoma: etiology, incidence and epidemiology. Curr Opin Urol 2004;14:229–33.
3. Mickisch GH. Multimodality treatment of metastatic renal cell carcinoma. Expert Rev Anticancer Ther 2002;2:681–5
4. Childs R, Chernoff A, Contentin N, et al. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral-blood stem-cell transplantation. N Engl J Med 2000;343:750–8.
5. Motzer RJ, Russo P. Systemic therapy for renal cell carcinoma. J Urol 2000;163:408–17.
6. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115–24.
7. Eton DT, Cella D, Bacik J, Motzer RJ. A brief symptom index for advanced renal cell carcinoma. Health Qual Life Outcomes 2006;4:68.
8. Bukowski RM. Natural history and therapy of metastatic renal cell carcinoma: the role of interleukin-2. Cancer 1997;80: 1198–220.
9. Ramsey S, Aitchison M. Treatment for renal cancer: are we beyond the cytokine era? Nat Clin Pract Urol 2006;3: 478–84.
10. Yang JC, Topalian SL, Parkinson D, et al. Randomized comparison of high-dose and low-dose intravenous interleukin-2 for the therapy of metastatic renal cell carcinoma: an interim report. J Clin Oncol 1994;12:1572–6.
11. Yang JC, Sherry RM, Steinberg SM, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol 2003;21:3127–32.
12. Mittal K, Wood L, Rini BI: Axitinib in metastatic renal cell carcinoma. Biol Ther 2012; 2(5)
13. Figlin RA HT, Tomczak P, Michaelson MD, Bukowski RM, Negrier S, Huang X, Kim ST, Chen I, Motzer RJ: Overall survival with sunitinib versus interferon (IFN)-alfa as first-line treatment of metastatic renal cell carcinoma (mRCC). J Clin Oncol 2008;26(Suppl):5024.
14. National Comprehensive Cancer Network (NCCN). Practice guidelines in oncology: kidney cancer (v.1.2008). accessed July 2013
15. Houk BE, Bello CL, Poland B, et al: Relationship between exposure to sunitinib and efficacy and tolerability endpoints in patients with cancer: results of a pharmacokinetic/ pharmacodynamic meta-analysis. Cancer Chemother Pharmacol 2010; 66:357-371.
16. Mittal K, Rini BI. Maintaining dose intensity and best supportive care: how important Is dose intensity and when is dose reduction the better strategy. Genitourinary Cancers Symposium Educational Summaries, 2013.
17. Wong MK, Mohamed AF, Hauber AB, et al: Patients rank toxicity against progression free survival in second-line treatment of advanced renal cell carcinoma. J Med Econ 2012; 15:1139–1148.
18. Motzer RJ, Hutson TE, Olsen MR, et al: Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol 2012;30:1371-1377.

19. Cella D, Kaiser K, Beaumont J, et al: Quality of life (QOL) among renal cell carcinoma (RCC) patients in a randomized double blind cross-over patient preference study of pazopanib versus sunitinib. ESMO Congress, 2012
20. Motzer RJ, Hutson TE, Reeves J, et al: Randomized open-label phase III trial of pazopanib versus sunitinib in first-line treatment of patients with metastatic renal cell carcinoma (MRCC): Results of the COMPARZ trial. ESMO Congress, 2012
21. O'Farrell AM, Abrams TJ, Yuen HA, et al: SU11248 is a novel FLT3 tyrosine kinase inhibitor with potent activity in vitro and in vivo. Blood 2003;101:3597-3605.
22. O'Farrell AM, Foran JM, Fiedler W, et al: An innovative phase 1 clinical study demonstrates inhibition of FLT3 phosphorylation by SU11248 in acute myeloid leukemia patients. Clin Cancer Res 2003;9:5465-5476.
23. Schueneman AJ, Himmelfarb E, Geng L, et al: SU11248 maintenance therapy prevents tumor regrowth after fractionated irradiation of murine tumor models. Cancer Res 2003;63:4009-4016.
24. Abrams TJ, Murray LJ, Pesenti E, et al: Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer. Mol Cancer Ther 2003;2:1011-1021.
25. Mendel DB, Laird AD, Xin X, Louie SG, Christensen JG, Li G, Schreck RE, Abrams TJ, Ngai TJ, Lee LB, Murray LJ, Carver J, Chan E, Moss KG, Haznedar JO, Sukbuntherng J, Blake RA, Sun L, Tang C, Miller T, Shirazian S, McMahon G, Cherrington JM. In vivo antitumor activity of SU11248, a novel tyrosine kinase inhibitor targeting vascular endothelial growth factor and platelet-derived growth factor receptors: determination of a pharmacokinetic/pharmacodynamic relationship. Clin Cancer Res 2003;9(1):327-37.
26. Faivre S, Delbaldo C, Vera K, et al. Safety, pharmacokinetic, and antitumor activity of SU11248, a novel oral multitarget tyrosine kinase inhibitor, in patients with cancer. J Clin Oncol 2006; 24:25-35.
27. Motzer RJ, Rini BI, Bukowski RM, Curti BD, George DJ, Hudes GR, Redman BG, Margolin KA, Merchan JR, Wilding G, Ginsberg MS, Bacik J, Kim ST, Baum CM, Michaelson MD. Sunitinib in patients with metastatic renal cell carcinoma. JAMA 2006 Jun 7;295(21):2516-24
28. Motzer RJ, Michaelson MD, Redman BG, Hudes GR, Wilding G, Figlin RA, Ginsberg MS, Kim ST, Baum CM, DePrimo SE, Li JZ, Bello CL, Theuer CP, George DJ, Rini BI. 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 2006;24(1):16-24.
29. Motzer RJ, Hutson, TE, Tomczak, P, et al. Overall survival and updated result with sunitinib compared with interferon (IFN)-alfa in patients with metastatic renal cell carcinoma (mRCC). J Clin Oncol 2009; 27:3584-3590.
30. Najjar YG, Elson P, Wood L, et al: Association of a 2-weeks-on and 1-week-off schedule of sunitinib with decreased toxicity in metastatic renal cell carcinoma. J Clin Oncol 2013; 31 (suppl 6; abstr 406).
31. Neri B, Vannini A, Brugia M, et al: Biweekly sunitinib regimen reduces toxicity and retains efficacy in metastatic renal cell carcinoma: A single-center experience with 31 patients. Int J Urol 2012;10.1111/j.1442-2042.
32. Atkinson BJ, Kalra S, Wang X, et al: A single-center retrospective review of outcomes associated with sunitinib alternative schedule compared to traditional schedule. J Clin Oncol 2013; 31(suppl 6; abstr 381).

33. Khalil B, Hudson JM, Williams R, et al: An individualized dose/schedule strategy for sunitinib in metastatic renal cell cancer (mRCC) on progression-free survival (PFS): Correlation with dynamic microbubble ultrasound (DCE-US) data. J Clin Oncol 2011; 29: (suppl; abstr e15149).
34. Webster K, Cell D, Yost K: The functional assessment of chronic illness therapy (FACIT) measurement system: properties, applications, and interpretation. Health and Quality of Life Outcomes 2003, 1:79
35. Sternberg CN, Davis ID, Mardiak J, et al: Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol 210; 28:1061-1068.
36. Eisen T, et al: Detailed comparison of the safety of tivozanib hydrochloride versus sorafenib in patients with advanced/metastatic renal cell carcinoma (mRCC) from a Phase III trial 2012 ESMO Congress. Presented October 2012.

APPENDIX 1: PILL DIARY

Patient Name or Initials: ____________________

Patient MRN# or Study ID#__________________

Sutent Diary Sheet

Sutent _______mg capsule

Take a total of _______capsule(s) daily for _______days with or without food then _____ days off therapy

Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____
Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____	Date______ Time______ Sutent_____
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Bring this diary sheet to every appointment

Reviewed by: ______________________________

Date of review: ____________________________

APPENDIX 2: BLOOD PRESSURE LOG

Name/MRN : _____

DATE Month/Date	TIME	BLOOD PRESSURE
	AM PM	
	AM PM	
	AM PM	
	AM PM	
	AM PM	
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*** **Please bring this diary card to all of your appointments**

Patient Signature and Date: _____

APPENDIX 3: FACT-G questionnaire

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4