Cover Page for Protocol

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A Phase II Randomized Controlled Trial

ASSET: Alternative Schedule Sunitinib in Metastatic Renal Cell Carcinoma – Cardiopulmonary Exercise Testing

DUKE CANCER INSTITUTE

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1 LIST OF ABBREVIATIONS

6MWD	6 Minute Walk Distance
AE	Adverse Event
BMI	Body Mass index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
COPD	Chronic Obstructive Pulmonary Disease
CrCl	Creatinine Clearance
CRF	Case Report Forms
CPC	Cancer Protocol Committee
CPET	Cardiopulmonary Exercise Testing
CSA	Cross-Sectional Area
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTQA	Duke Clinical Trials Quality Assurance
DBP	Diastolic Blood Pressure
DCI	Duke Cancer Institute
DE	Dimensional Echocardiography
DSMB	Data Safety Monitoring Board
DUHS	Duke University Health System
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FDA	Federal Drug Administration
FKSI-19	Functional Assessment of Cancer Therapy-Kidney Symptom Index -19
GCP	Good Clinical Practice
GLS	Global Longitudinal Strain
HADS	Hospital Anxiety and Depression Scale
HIFα	Hypoxia-Inducible Factor alpha
HRQL	Health-related Quality of Life
ICH	International Conference on Harmonization
IFNα	Interferon alpha
IMDC	International Metastatic Database Consortium
IRB	Institutional Review Board
ITT	Intent to treat
KPS	Karnofsky Performance Status
LDH	Lactate Dehydrogenase
LVCF	Last Value Carried Forward
LVEF	Left ventricular ejection fraction
mOS	Median Overall Survival
mPFS	Median Progression Free Survival
mRCC	Metastatic Renal Cell Carcinoma
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian Target Of Rapamycin
NCCN	National Comprehensive Cancer Network
NYHA	New York Heart Association
OS	Overall Survival
PDGFR	Platelet-derived Growth Factor Receptor

PI	Principal Investigator
QOL	Quality Of Life
RCC	Renal Cell Carcinoma
RTKs	Receptor Tyrosine Kinases
SBP	Systolic Blood Pressure
SI	International System of Units
SOC	Safety Oversight Committee
SOP	Standard Operating Procedures
TFT	Thyroid Function Test
TKI	Tyrosine Kinase Inhibitor
TUP	Timed Get Up and Go
ULN	Upper Limit of Normal
UPC	Urine Protein Creatinine Ratio
U.S.	United States
VEGF	Vascular Endothelial Growth Factor
VO_2peak	Peak Oxygen Uptake

2 STUDY SCHEMA

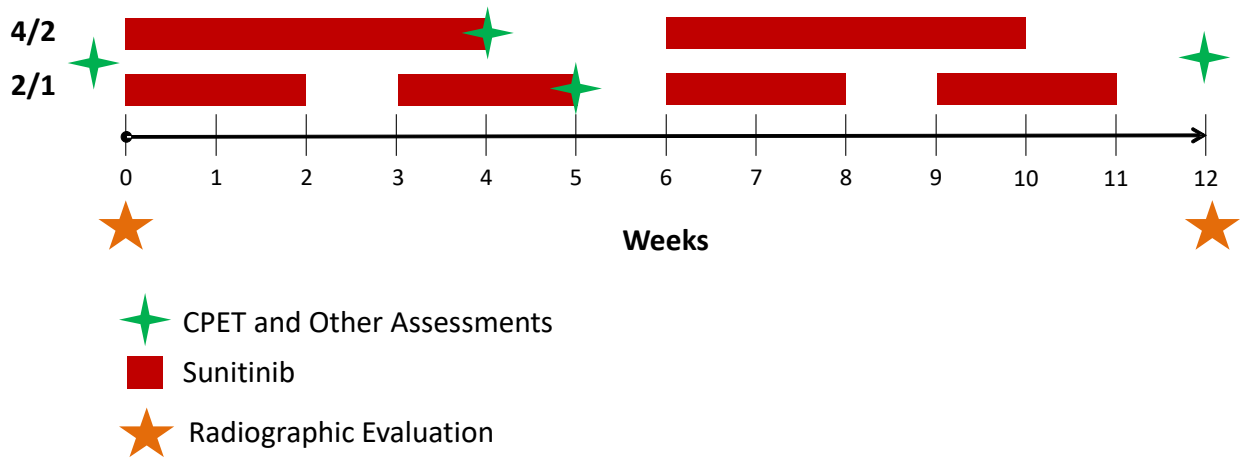
Objective: To investigate changes in cardiopulmonary function in patients treated with sunitinib for metastatic renal cell carcinoma (RCC) on schedule 4/2 and schedule 2/1.

Design: Patients with histologically confirmed, treatment-naive metastatic RCC (mRCC), good or intermediate Heng Risk, and Karnofsky Performance Status (KPS) ≥ 80will be enrolled. To be eligible, patients must also have no contraindications to maximal exercise testing and must complete satisfactory exercise testing at baseline.

- Cardiopulmonary exercise testing (CPET) will be performed at baseline, as well as during sunitinib treatment, in order to document changes in peak oxygen consumption (VO_2peak) on each arm.
- Primary determinants of VO_2peak, dose intensity of sunitinib, treatment-emergent adverse events (AE), and patient-reported outcomes will also be assessed at similar time points.

Subjects will be randomly allocated to sunitinib treatment at 50 mg daily on one of the two following arms:

A. Schedule 4/2 (n=15) or
B. Schedule 2/1 (n=15)



3 BACKGROUND AND SIGNIFICANCE

3.1 Renal Cell Carcinoma: Background and Standard Treatments

Renal cell carcinoma accounts for ~3% of all cancers in the United States. This translates to 63,000 new cases a year with 14,000 associated deaths.[1] Metastatic disease is found in 30% of subjects at diagnosis. Close to 90-95% of metastatic disease is of the clear-cell histology.[2] Multiple scoring systems are available to characterize prognosis in treatment-naive RCC. Two of the most commonly used scoring systems are the Memorial Sloan-Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC).[3,4] Each of these systems categorizes patients as favorable, intermediate, or poor risk based on how many adverse prognostic factors are present (0: favorable risk; 1-2: intermediate risk; 3 or more: poor risk).

The five parameters included in the MSKCC prognostic score are KPS, nephrectomy status, hemoglobin value, LDH, and corrected calcium concentration. Time from diagnosis to treatment is often used in place of nephrectomy status. The six parameters of importance for IDMC prognostic score classification are Karnofsky Performance Status (KPS), time from diagnosis to treatment, hemoglobin value, corrected calcium concentration, absolute neutrophil count, and platelet count. With each system, total number of adverse prognostic factors present has been shown to correlate with overall survival. Approximately 25% of patients are in the favorable-risk group, 50% are in the intermediate-risk group, and 25% are in the poor-risk group. In an analysis of 1028 patients scored using the IMDC system, median OS for favorable-, intermediate-, and poor-risk patients is 43.2 months, 22.5 months, and 7.8 months, respectively.[5]

Until recently, the cytokines IL-2 and IFN-α were the only active treatments for advanced or metastatic RCC. However, due to each of these agents' limited clinical benefit and substantial toxicity profile, newer targeted agents have largely replaced cytokines in the treatment of advanced or mRCC.[6-8] The recognition of the importance of hypoxia-inducible factor alpha (HIFα) signaling in the pathogenesis of clear-cell RCC has led to widespread study of two classes of targeted therapies: anti-angiogenic agents and mTOR inhibitors.[9] Targeting of angiogenesis is rational because constitutive HIFα activation leads to the upregulation or activation of several proteins including vascular endothelial growth factor (VEGF), which can subsequently lead to tumor proliferation and neovasculature formation. Targeting of the mTOR pathway is important because activation of the upstream PI3K/Akt/mTOR signaling pathway is one method by which constitutive HIFα activation or upregulation occurs.

There are 8 targeted agents approved for the treatment of RCC in the United States: 5 that target angiogenesis (i.e., the VEGF-receptor tyrosine kinase inhibitors sorafenib, sunitinib, pazopanib, axitinib, and the VEGF-binding monoclonal antibody bevacizumab), 2 that target the mTOR pathway (i.e., everolimus and temsirolimus), and 1 that targets an immune checkpoint (i.e., the PD-1 inhibitor nivolumab). Among these approved agents, none have demonstrated a statistically significant improvement in overall survival (OS) except for temsirolimus poor-risk patients and nivolumab in VEGF-refractory patients. According to National Comprehensive Cancer Center Network (NCCN) guidelines, sunitinib, temsirolimus (poor risk only), bevacizumab plus interferon, and pazopanib are Category 1 recommendations for first-line therapy of mRCC.[10]

3.2 Study Agent – Sunitinib in Renal Cell Carcinoma

Sunitinib is a VEGF receptor TKI that is approved and recommended for the treatment of mRCC across prognostic groups.[10] In a randomized Phase 3 trial of sunitinib vs. IFNα in treatment-naive subjects, median progression free survival (mPFS) and median OS (mOS) were greater in the sunitinib group than in the IFNα group (mPFS: 11 mo vs. 5 mo, HR = 0.539; p = < .001); mOS: 26.4 mo vs. 21.8 mo, HR = 0.821; p = .051).[11] The overall response rate (ORR) was also greater in the sunitinib group (47%) than in the IFNα group (12%). More recently, sunitinib was compared to pazopanib in treatment-naïve subjects in the Phase 3 COMPARZ study.[12] In this non-inferiority study, sunitinib and pazopanib demonstrated similar mPFS (8.4 mo for pazopanib vs. 9.5

mo for sunitinib, HR = 1.05) and mOS (28.4 mo for pazopanib vs. 29.3 mo for sunitinib, HR = 0.91; p = 0.28). The ORR of pazopanib and sunitinib was 31% and 24%, respectively. The most common (≥ 20) adverse reactions include fatigue, generalized muscle weakness, fever, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, peripheral edema, rash, hand-foot syndrome, skin discoloration, dry skin, hair color changes, altered taste, headache, back pain, arthralgia, extremity pain, cough, dyspnea, anorexia, and bleeding [Sunitinib (Sutent®) U.S. Prescribing Information, April 2015]. Other important adverse reactions include hepatotoxicity, QT prolongation (including Torsades de Pointes), osteonecrosis of the jaw, tumor lysis syndrome, and thyroid dysfunction.

3.3 Study Purpose/Rationale

Schedule 2/1: An Important Alternative Dosing Regimen of Sunitinib

A key challenge with sunitinib therapy for mRCC is to maximize quality of life (QOL) by minimizing toxicity without compromising efficacy. Specifically, maintenance of sunitinib dose intensity is related to improved clinical outcomes.[13] A recent Phase III trial provides an example of these difficulties: fatigue was one of the most common treatment-emergent adverse events (AEs), with 63% of sunitinib-treated patients experiencing fatigue, including 17% with grade 3/4 fatigue.[12] Interestingly, 49% of sunitinib-treated patients required dose interruptions of ≥7 days, and 51% required dose reductions; 20% discontinued treatment due to AEs. More work is clearly needed to achieve this delicate balance.

Preliminary evidence suggests that the alternative schedule 2/1 of sunitinib may maximize both efficacy and tolerability. In theory, schedule 2/1 (2-weeks on, 1-week off) results in more frequent dose interruptions than the standard schedule 4/2 (4-weeks on, 2-weeks off) without affecting dose intensity over the same six-week period. In practice, however, schedule 2/1 may achieve better dose intensity. Multiple retrospective studies comprising over 700 patients have suggested that switching from the standard 4/2 schedule to the alternative 2/1 schedule is associated with both improved outcomes and toxicity profile.[14-18] Four sets of observations may explain these findings.

- First, maximizing the dose intensity of sunitinib is associated with improved clinical outcomes (PFS and OS).[13]
- Second, both steady state of sunitinib and optimal inhibition of vascular perfusion are reached after 2 weeks.[17,19]
- Third, an increased compensatory angiogenic response (proliferation of endothelial cells) has been associated with increased time off of sunitinib therapy.[20,21]
- Fourth, AEs such as fatigue were typically the impetus for dose/schedule modification from schedule 4/2 in the retrospective studies. AEs improved with modification, potentially resulting in fewer dose interruptions and discontinuations due to toxicity.[14-18]

For example, Atkinson et al demonstrated that the most common AE associated with schedule modification was fatigue (64%), which was reduced to 29% upon follow up after schedule modification.[14] In this study alternative schedule sunitinib, comprised mostly of schedule 2/1 (82%), was also associated with at least comparable time on treatment, PFS, and OS. Further prospective evaluation of sunitinib schedule 2/1 is clearly warranted.

To this end, two prospective single-arm studies are ongoing: (1) to evaluate the tolerability of the 2/1 schedule compared with historical controls (NCT02060370), and (2) to study individualized dosing of sunitinib, including dose reduction to the 2/1 schedule in those who experience treatment-emergent toxicity (NCT01499121). While these studies will provide prospective safety and efficacy data on schedule 2/1, neither trial is comparative or quantitates the functional consequences of treatment-emergent AEs.

Clinical Importance of VO_2peak

Cardiorespiratory fitness testing provides a unique way to measure the tolerability and physiological effects of cancer therapy. The gold standard for direct assessment of cardiorespiratory fitness is peak oxygen consumption (VO_2peak). As measured by an objective exercise tolerance test (CPET), VO_2peak reflects the integrative ability of the cardiopulmonary system to deliver adequate oxygen and substrate to metabolically active skeletal muscles for ATP resynthesis.[22] Measured or estimated VO_2peak is a well-established independent predictor of mortality in a broad range of non-cancer populations.[23,24] In a series of studies, measurement of VO_2peak has also been demonstrated to be safe and well-tolerated in a wide range of cancer patients both during and following therapy.[25-28] Both a diagnosis of cancer and its associated therapeutic management are associated with significant impairments in VO_2peak,[29-31] while low VO_2peak is a significant predictor of physical and functional QOL domains, fatigue, and other patient reported outcomes (PROs).[32,33] For example, for a given age group (i.e., 60 year olds), compared with healthy women with no diagnosis of breast cancer, patients with breast cancer reached a given VO_2peak value about 20 to 30 years earlier. This amounts to "physiologic aging" of several decades in the women with cancer. Finally, VO_2peak was demonstrated to be a significant predictor of *overall mortality* in cancer patients, providing prognostic information beyond established factors including performance status.[25,34] In summary, VO_2peak may be an important quantitative marker of change in function due to cancer therapy and is associated with survival in patients with cancer.

Summary: Rationale & Hypothesis

While 4/2 is the recommended starting sunitinib dosing schedule in mRCC, retrospective evidence exists suggesting that schedule 2/1 may be at least as efficacious with an improved safety profile. However, no prospective data exists comparing the two schedules in terms of tolerability. Studies are needed to quantitate the functional cardiovascular and muscular changes induced by these two regimens. Specifically, the phenomenology of fatigue in this setting needs to be better understood. Our overall hypothesis is that schedule 2/1 of sunitinib is not only better tolerated but will be associated with less fatigue and functional cardiovascular/muscular toxicity than the 4/2 schedule. In this study, the first in a continuum of research, we will obtain data on the magnitude of VO_2peak decline (mean, median, standard deviation, etc.) in each arm in order to design a more definitive study to test this hypothesis. Because future studies will include exercise training as a component, data on physiological determinants of VO_2peak will be useful to design an optimal exercise training program.

4 OBJECTIVES AND ENDPOINTS

All endpoints will be evaluated at the time points specified in the Schedule of Events at the beginning of **Section 8**. See **Section 11** for Statistical Methods and Data Analysis. Key comparisons will be the change from Day 1 (week 1) to Day 85 (through week 12).

	Objective	Endpoint	Analysis
Primary	To estimate the change in VO_2peak after 12 weeks from baseline in treatment-naïve mRCC patients treated with sunitinib on schedule 4/2 and 2/1	Change in VO_2peak with sunitinib on schedule 4/2 or 2/1 after 12 weeks from baseline	See **Section 11.1** to **Section 11.4**
Key Secondary	To assess the effects on the primary physiological determinants of VO_2peak (e.g., resting and stress cardiac function and muscle function, defined as cross-sectional area,	• Rest and Exercise Left Ventricular Ejection Fraction (LVEF) and Cardiac Function by 2-D and 3-D echocardiography (2DE/3DE) including Global Longitudinal Strain (GLS)	See **Section 11.5**

	Objective	Endpoint	Analysis
	strength endurance and maximal strength)	• Upper and lower extremity maximal muscular strength: o voluntary one-repetition maximum (1-RM) o muscular endurance (number of repetitions to fatigue at 70% of 1-RM) • Muscle cross-sectional area (CSA) of the major muscles near L3 (CT scans and Slice-O-Matic® software)	
Other Secondary	To evaluate changes in other measures of physical functioning/functional capacity and correlate with changes in VO_2peak	Objective assessments (i.e., chair-stand test, timed up and go, 6-minute walk distance) of functional capacity	See **Section 11.5**
Other Secondary	To estimate the effects on patient-reported outcomes (i.e., fatigue and QOL)	Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (FKSI-19)- Godin Leisure Time Exercise Questionnaire	See **Section 11.5**
Other Secondary	To evaluate co-existent depression	Hospital Anxiety and Depression Scale (HADS)	See **Section 11.5**
Exploratory	To evaluate safety and tolerability of both: (a) Sunitinib and (b) Exercise testing	Eligibility rate, attrition rate, and adverse event rate (CTCAE v4.0) in each arm	See **Section 11.5**
Exploratory	To determine the dose intensity of sunitinib	Patient- reported drug diaries	See **Section 11.5**
Exploratory	To estimate early change in VO_2peak at 4-5 weeks compared with baseline	Change in VO_2peak from baseline to 4-5 weeks	See **Section 11.5**
Exploratory	To collect plasma angiome samples for analysis and correlation with primary and key secondary endpoints	Plasma angiome multiplex ELISA	See **Section 11.5**
Exploratory	To use real-time electronic monitoring to describe the following over the study period (subset of patients): (a) Changes in daily physical activity (b) Changes in daily blood pressure	(a) Steps per day (b) Daily blood pressure (mmHg) reading	See **Section 11.5**

5 INVESTIGATIONAL PLAN

5.1 Study Design

Proposed is a randomized (1:1) prospective trial to determine changes in VO_2peak in patients with treatment-naïve mRCC treated with sunitinib therapy on two different common schedules (see **Section 2**). Patients randomized to sunitinib schedule 4/2 (**Arm A**) will receive sunitinib at 50 mg daily for 4 weeks on, followed by 2 weeks off, per standard of care. Patients randomized to sunitinib schedule 2/1 (**Arm B**) will receive sunitinib 50 mg daily for 2 weeks on, followed by 1 week off. All subjects will undergo detailed functional capacity assessments at baseline, 4-5 weeks, and after 12 weeks.

Specific recommendations for management of possible AEs, along with guidelines for dose delay/modification or discontinuation from study treatment are provided in this section, based on best evidence from contemporary trials and retrospective studies.[12,15]

5.1.1 Dose Modification

Dose interruptions or reductions of sunitinib may be required following potential drug-related toxicities. Fatigue, generalized muscle weakness, mucositis/stomatitis, hypertension, hand-foot syndrome, bleeding, vascular thrombosis, thrombocytopenia/neutropenia, and other AEs have been reported in response to treatment with sunitinib.[35]

At each visit during the Treatment Period, subjects should first be evaluated for the occurrence of AEs and laboratory abnormalities. Specific recommendations for management of possible AEs, other than hepatoxicity, along with guidelines for dose delay/modification or discontinuation of study treatment, are adapted from Kollmannsberger et al.,[36] and are provided in **Table 1**. In the event of treatment-emergent hepatotoxicity, please follow the guidelines for management hepatotoxicity provided in **Table 2**. For toxicities unrelated to sunitinib, dose modifications and holds are per the discretion of the investigator.

If dose reduction is necessary, two dose reductions are permitted in a stepwise fashion (initially to 37.5 mg and subsequently to 25 mg if necessary); however, the schedule (4/2 vs. 2/1) will not be changed during the study period. If the toxicity does not recur or worsen, the dose can then be increased stepwise back to the next dose level (37.5 mg or 50 mg as appropriate) at the start of the next treatment cycle. Increases to the next dose level should only be initiated at the start of the next treatment cycle, not during a treatment cycle.

Table 1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events (AEs)

AE Terms & Descriptions	Dose Modification Algorithms	
	Sunitinib 4/2	**Sunitinib 2/1**
Hypertension (Scenario)		
(A). Asymptomatic and persistent systolic blood pressure (SBP) of ≥150 and <170 mmHg, or diastolic blood pressure (DBP) of ≥90 and <110 mmHg, or a clinically significant increase in DBP of ≥20 mmHg.	Step 1. Continue study treatment at same dose. Step 2. Adjust current dose of or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[1] blood pressure (BP). If BP is not well-controlled within 2 weeks, follow Step 1 in scenario (B) below.	Step 1. Continue study treatment at same dose. Step 2. Adjust current dose of or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[1] blood pressure (BP). If BP is not well-controlled within 2 weeks, follow Step 1 in scenario (B).
(B). Symptomatic, or SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1. Interrupt study treatment. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Restart study treatment at same dose or lower dose at discretion of investigator[2] once BP is well-controlled.[1] Dose adjustment or discontinuation of antihypertensive medication(s) may be necessary during scheduled 2-week off treatment period.	Step 1. Interrupt study treatment. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Restart study treatment at same dose or lower dose at discretion of investigator[2] once BP is well-controlled.[1] Dose adjustment or discontinuation of antihypertensive medication(s) may be necessary during scheduled 1-week off treatment period.
(C). Two or more symptomatic episodes of hypertension despite modification of antihypertensive medication(s) and reduction of study medication dose.	Discontinue study treatment and follow up per protocol.	Discontinue study treatment and follow up per protocol.
Cardiac Toxicity		
Grade 1	Continue at same dose level	Continue at same dose level
Grade 2	Continue at same dose level. *OR* If asymptomatic decrease of LVEF by absolute value of 20% and to <LLN or nonurgent ventricular paroxysmal dysrhythmia requiring intervention: Step 1. Interrupt study treatment until toxicity reduced to ≤ Grade 1. Step 2. Restart treatment with lower dose[2]; monitor as clinically indicated.	Continue at same dose level. *OR* If asymptomatic decrease of LVEF by absolute value of 20% and to <LLN or nonurgent ventricular paroxysmal dysrhythmia requiring intervention: Step 1. Interrupt study treatment until toxicity reduced to ≤ Grade 1. Step 2. Restart treatment with lower dose[2]; monitor as clinically indicated.
Grade 3	Step 1. Interrupt study treatment until toxicity reduced to ≤ Grade 1. Step 2. Restart treatment with lower dose[2]; monitor as clinically indicated.	Step 1. Interrupt study treatment until toxicity reduced to ≤ Grade 1. Step 2. Restart treatment with lower dose[2]; monitor as clinically indicated.
Grade 4	Discontinue study treatment and follow up per protocol.	Discontinue study treatment and follow up per protocol.

AE Terms & Descriptions	Dose Modification Algorithms	
	Sunitinib 4/2	**Sunitinib 2/1**
Proteinuria		
Urine Protein Creatinine Ratio (UPC) <3	Continue study treatment at same dose. Monitor as clinically indicated.	Continue study treatment at same dose. Monitor as clinically indicated.
UPC ≥3	Step 1: Obtain a 24-hr urine protein. Step 2: If 24-hour urine protein is <3 g, subject may continue treatment at same dose. OR If 24-hour urine protein is ≥3 g, interrupt treatment until UPC returns. to <3. Restart therapy at lower dose.[2] Monitor UPC for the remainder of the overall treatment period. If UPC ≥3, obtain a 24- hour urine protein. Step 3: If 24-hour urine protein is ≥3 g, following repeat dose reductions, discontinue treatment and follow up per protocol.	Step 1: Obtain a 24-hr urine protein. Step 2: If 24-hour urine protein is <3 g, subject may continue treatment at same dose. OR If 24-hour urine protein is ≥3 g, interrupt treatment until UPC returns. to <3. Restart therapy at lower dose.[2] Monitor UPC for the remainder of the overall treatment period. If UPC ≥3, obtain a 24- hour urine protein. Step 3: If 24-hour urine protein is ≥3 g, following repeat dose reductions, discontinue treatment and follow up per protocol.
Hemorrhage/Bleeding/Coagulopathy		
Grade 1	Continue study treatment at same dose. Monitor as clinically indicated.	Continue study treatment at same dose. Monitor as clinically indicated.
Grade 2	Step 1. Interrupt study treatment until the AE resolves to ≤ Grade 1. Step 2. Restart treatment with lower dose2; monitor as clinically indicated.	Step 1. Interrupt study treatment until the AE resolves to ≤ Grade 1. Step 2. Restart treatment with lower dose2; monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥Grade 2 event after dose interruption/reduction.	Discontinuation of study treatment and follow up per protocol. **Note:** If abnormality is not clearly associated with clinical consequences, contact the Duke PI to discuss the potential for continuation of study treatment. If agreed, subject may restart treatment at lower dose.[2]	Discontinuation of study treatment and follow up per protocol. **Note:** If abnormality is not clearly associated with clinical consequences, contact the Duke PI to discuss the potential for continuation of study treatment. If agreed, subject may restart treatment at lower dose.[2]

AE Terms & Descriptions	Dose Modification Algorithms	
	Sunitinib 4/2	**Sunitinib 2/1**
Venous Thrombosis		
Grade 2	Continue study treatment with same dose; monitor as clinically indicated.	Continue study treatment with same dose; monitor as clinically indicated.
Grade 3 or asymptomatic Grade 4	Step 1. Interrupt study treatment. Step 2. Start to treat the subject with an anticoagulant. Step 3. Resume study treatment at same dose during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have been treated with anticoagulant for at least one week. • No Grade 3 or 4 hemorrhagic events have occurred while on anticoagulation treatment. • Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.	Step 1. Interrupt study treatment. Step 2. Start to treat the subject with an anticoagulant. Step 3. Resume study treatment at same dose during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have been treated with an anticoagulant for at least one week. • No Grade 3 or 4 hemorrhagic events have occurred while on anticoagulation treatment. • Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment.
Symptomatic Grade 4	Discontinuation of study treatment and follow up per protocol.	Discontinuation of study treatment and follow up per protocol
Arterial Thrombosis		
Any Grade	Discontinuation of study treatment and follow up per protocol.	Discontinuation of study treatment and follow up per protocol
Neutropenia		
Grade 1 or 2	Continue study treatment at same dose; monitor as clinically indicated.	Continue study treatment at same dose; monitor as clinically indicated.
Grade 3 lasting ≥5 days	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at same dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at same dose.
Grade 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]
Recurrent Grade 3/4 event after initial dose reduction	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lowest dose (25 mg/day).	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lowest dose (25 mg/day).

AE Terms & Descriptions	Dose Modification Algorithms	
	Sunitinib 4/2	**Sunitinib 2/1**
Thrombocytopenia		
Grade 1 or 2	Continue study treatment at same dose; monitor as clinically indicated.	Continue study treatment at same dose; monitor as clinically indicated.
Grade 3 lasting ≥5 days	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]
Grade 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lower dose.[2]
Recurrent Grade 3/4 event after initial dose reduction	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lowest dose (25 mg/day).	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment with lowest dose (25 mg/day).
Fatigue (lethargy, malaise, generalized muscle weakness)[3]		
Grades 1 and 2	Continue study treatment at same dose; monitor as clinically indicated	Continue study treatment at same dose; monitor as clinically indicated.
Grades 3 and 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose.[2]
Hand-foot Syndrome		
Grades 1 and 2	Continue study treatment at same dose; monitor as clinically indicated.	Continue study treatment at same dose; monitor as clinically indicated.
Grade 3	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at same dose or lower dose at discretion of investigator.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at same dose or lower dose at discretion of investigator.[2]
Grade 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose or discontinue at discretion of investigator.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose or discontinue at discretion of investigator.[2]
Anemia: **Note:** No dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above		

AE Terms & Descriptions	Dose Modification Algorithms	
	Sunitinib 4/2	**Sunitinib 2/1**
Other Clinically Significant Adverse Events[4]		
Grade 1 or 2	Continue study treatment at same dose; monitor as clinically indicated.	Continue study treatment at same dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at same dose or lower dose at discretion of investigator.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at same dose or lower dose at discretion of investigator.[2]
Recurrent Grade 3	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at lower dose.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 1. Step 2. Restart study treatment at lower dose.[2]
Grade 4	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose or discontinue at discretion of investigator.[2]	Step 1. Interrupt study treatment until toxicity reduced to ≤Grade 2. Step 2. Restart study treatment at lower dose or discontinue at discretion of investigator.[2]

1. Well-controlled BP defined as mean SBP <150 mmHg and mean DBP <90 mmHg. See **Appendix F: Recommendations for Management of Hypertension**.
2. Sunitinib dose should be reduced by 12.5 mg (i.e., 50 mg to 37.5 mg or 37.5 mg to 25 mg), but the schedule (i.e., 4/2 or 2/1) MUST be maintained.
3. See **Section 5.2.1** for additional guidelines on management of fatigue and generalized muscle weakness.
4. Adverse events are graded according to NCI Common Terminology Criteria for Adverse Events v4.0

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

5.1.2 Dose Modifications and Management of Liver Toxicity

In the event of treatment-emergent hepatotoxicity, potential contributing factors such as concomitant medications, viral hepatitis, choledocholithiasis, and hepatic metastases should be investigated. Concomitant medications known to be hepatotoxic that may be contributing to liver dysfunction should be discontinued or replaced with alternative medications to allow for recovery of liver function. As generally understood, ALT >3 x upper limit of normal (ULN) and concomitant bilirubin ≥2.0 x ULN (>35% direct bilirubin), in the absence of elevated alkaline phosphatase or biliary injury, suggest significant liver injury. See **Table 2: Guidelines for Management of Treatment-Emergent Hepatotoxicity**.

Table 2 Guidelines for Management of Treatment-Emergent Hepatotoxicity

AE Terms & Descriptions	Dose Modification Algorithms
(A). ALT of ≤3.0 x ULN	Continue study treatment with full-panel liver function tests (LFTs)[1] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	Continue study treatment. Perform the following assessments for excluding hypersensitivity and other contributing factors: • Eosinophil count • Viral serology for hepatitis A, B, and C • Liver imaging Monitor subject closely for clinical signs and symptoms; perform full-panel LFTs[1] weekly or more frequently if clinically indicated until ALT/AST reduced to Grade 1. If the subject is withdrawn from study treatment, follow up per protocol.
(C). ALT >3.0 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN; **with** direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash) Or (D). ALT >8.0 x ULN **without** concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN; **with** direct bilirubin >35%)	Discontinue study treatment immediately. Consult a hepatologist, and perform the following assessments to identify co-contributing factors: • Eosinophil count • Viral serology for hepatitis A, B, C, and E; cytomegalovirus (CMV); Epstein-Barr virus (EBV IgM antibody, or heterophile antibody, or monospot testing); anti-nuclear antibody (ANA); anti-smooth muscle antibody (SMA); and anti- mitochondrial antibody • Serum creatinine phosphokinase (CPK) for possible muscle injury • LFT elevation • Liver imaging (ultrasound or CT scan) Monitor subject closely for clinical signs and symptoms; perform full-panel LFTs[1] weekly or more frequently if clinically indicated until LFTs reduced to Grade 1.
Isolated total bilirubin elevation without concurrent ALT elevation (defined as ALT <3 x ULN)	Step 1. Perform bilirubin fractionation at any time when total bilirubin is ≥1.5 X ULN. Continue dosing at full dose, and perform weekly LFT assessments[1] until total bilirubin return to ≤1.5 x ULN.

1. Full-panel LFTs include: AST, ALT, alkaline phosphatase, γ-GT, and total bilirubin. If at any time the total bilirubin is > 1.5 x ULN, perform bilirubin fractionation for direct and indirect bilirubin.

Note: Because many subjects are taking multiple concurrent medications, it is critical to do a thorough evaluation of the subject's concurrent medications, identify and discontinue those with known hepatotoxicity, and replace with a non-hepatotoxic equivalent for the same indication if necessary.

5.2 Subject Monitoring and Management Guidelines for Certain Treatment-Emergent Adverse Events (AEs) of Interest

5.2.1 Fatigue and Generalized Muscle Weakness

Fatigue and generalized muscle weakness are commonly reported symptoms in patients with cancer. Both fatigue and generalized muscle weakness have been reported with sunitinib and other angiogenesis inhibitors in this class. Although the etiology of these events is generally unknown, hypothyroidism has been reported with this class of agents [Rini, 2007] and may be a contributing factor in some patients with fatigue and generalized muscle weakness.

To avoid any delay in the treatment of easily manageable conditions such as electrolyte disorders and to quickly recognize possible serious conditions such as cardiac dysfunction, the following steps are recommended when caring for subjects with fatigue and generalized muscle weakness. Subjects complaining of grade 2, 3, or 4 fatigue and/or generalized muscle weakness should be investigated as appropriate including the following suggested workup outlined below.

- Subjects with grade 3 or more fatigue and/or generalized muscle weakness should be seen immediately.
- A workup should include a detailed history and physical examination, measurement of serum electrolytes, liver function tests, an electrocardiogram, chest X-ray, thyroid function tests, and an early-morning cortisol.
- Electrolyte abnormalities should be supplemented and adrenal insufficiency or hypothyroidism should be treated with replacement therapy.
- An ACTH stimulation test should be performed if the cortisol concentration is <10 mcg/dL (280 nmol/L).
- If the subject's history or physical examination points toward symptoms or signs of congestive heart failure, the appropriate investigations should be performed including an echocardiogram.
- Subjects should be closely monitored on a weekly basis or more frequently if clinically indicated for duration of severe fatigue and generalized muscle weakness.
- Sunitinib dose (but *not* schedule) should be adjusted according to the dose adjustment guidelines in **Table 1: Dose Modification Algorithms for Potential Treatment-Related Adverse Events (AEs)**.

Please contact the Duke PI if you require further guidance.

5.2.2 Abdominal Pain

Abdominal pain is a common symptom with vascular endothelial growth factor (VEGF) receptor antagonists, including sunitinib. Bowel perforations have been reported in clinical trials of pazopanib, sunitinib, and with other agents in this class. Bowel perforations have been associated in some patients with tumor in the bowel wall, or diverticulitis, while in others there has been no clear explanation.

Although bowel perforation is a rare event, investigators and study staff at the site are advised to be vigilant of this potential complication in subjects receiving sunitinib. Please contact the Duke PI if you need further guidance or would like to discuss an event involving abdominal pain or bowel perforations.

5.3 Treatment Compliance

5.3.1 Missed Doses

Missed doses of sunitinib will be skipped, the subject should resume dosing the next day, and this should be recorded in the Pill Diary.

5.3.2 Concomitant Medications

All concomitant medications must be recorded on the appropriate case report form (CRF) and will be assessed at each study-related clinic visit.

5.3.2.1 Effects of Sunitinib on Exposure to Other Drugs

In vitro studies indicated that sunitinib does not induce or inhibit major cytochrome P450 (CYP) enzymes. The *in vitro* studies in human liver microsomes and hepatocytes of the activity of CYP isoforms CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and CYP4A9/11 indicated that sunitinib and its primary active metabolite are unlikely to have any clinically relevant drug-drug interactions with drugs that may be metabolized by these enzymes.[35]

See the sunitinib package insert[35] for full details:
http://www.labeling.pfizer.com/ShowLabeling.aspx?id=607#S7.1

5.3.2.2 Drugs That May Affect Exposure to Sunitinib

CYP3A4 Inhibitors

Strong CYP3A4 inhibitors such as ketoconazole may increase sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of sunitinib with the strong CYP3A4 inhibitor, ketoconazole, resulted in 49% and 51% increases in the combined (sunitinib + primary active metabolite) Cmax and AUC0–∞ values, respectively, after a single dose of sunitinib in healthy volunteers. Co-administration of sunitinib with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase sunitinib concentrations. Grapefruit may also increase plasma sunitinib concentrations. **A dose reduction for sunitinib should be considered when it must be co-administered with strong CYP3A4 inhibitors**.[35]

CYP3A4 Inducers

CYP3A4 inducers such as rifampin may decrease sunitinib plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of sunitinib with the strong CYP3A4 inducer, rifampin, resulted in a 23% and 46% reduction in the combined (sunitinib + primary active metabolite) Cmax and AUC0–∞ values, respectively, after a single dose of sunitinib in healthy volunteers. Co-administration of sunitinib with inducers of the CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease sunitinib concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. Patients receiving sunitinib should not take St. John's Wort concomitantly. **A dose increase for sunitinib should be considered when it must be co-administered with CYP3A4 inducers**.[35]

5.3.2.3 Precautions Regarding Concomitant Medications

Refer to the following links for updated lists of CYP inhibitors and inducers:

- http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#potency
- http://medicine.iupui.edu/clinpharm/ddis/table.aspx

See also the sunitinib package insert:[35]
http://www.labeling.pfizer.com/ShowLabeling.aspx?id=607#S7.1

5.3.3 Randomization

When the subject has been registered, has completed screening, and has been found eligible post-baseline testing, the study coordinator will request the subject's random assignment to one of the two treatment arms from the Medidata RAVE database.

For this pilot study, subjects will be randomly assigned (randomized) with equal probability to either sunitinib schedule 4/2 or 2/1. This study is open label, meaning that neither subjects nor study personnel will be blinded to treatment assignment.

Note: For subjects who are not eligible and fail the screening process, no further action is necessary and no additional information will be collected. However, the number of screen failures and reason for screen failure will be collected and tallied at the end of the study.

Case report forms will only be completed for those registered and randomized subjects, including those who do not receive treatment. However, subjects who do not receive the assigned treatment will be replaced and not counted toward the overall study sample size. Data limited to demographics and reason for screen failure will be collected for screen failures.

5.4 Rationale for Selection of Dose, Regimen, and Treatment Duration

Sunitinib has an indication for the treatment of advanced RCC.[35] The FDA-approved dose of sunitinib for advanced RCC is one 50 mg oral dose taken once daily, on a treatment schedule of 4 weeks on followed by 2 weeks off (schedule 4/2), which is the dose that will be used in **Arm A** for this study.

Sunitinib packaging (4/2015) states, "In patients with advanced RCC who are unable to tolerate Schedule 4/2, consider the dose reduction described in the FDA-approved label or, as an alternative, consider modifying the schedule to 2 weeks on treatment followed by 1 week off (Schedule 2/1) using the same dose.

—"Studies supporting Schedule 2/1 have not been reviewed by the FDA. For most studies, the patient population was small and/or analysis was post hoc, and therefore susceptible to bias. The efficacy of any particular alternative dosing schedule has not been established."
https://www.pfizerpro.com/product/sutent/advanced-rcc/dosing#dm

Schedule 2/1 will be used in **Arm B** for this study. **Note:** The dose intensity for a 6-week period is the same for schedule 4/2 and 2/1 (50 mg/day * 28 days = 1400 mg).

5.5 Rationale for Study Evaluations

PRIMARY PHYSIOLOGICAL DETERMINANTS OF VO_2peak

Rest and Exercise Left Ventricular Ejection Fraction and Cardiac Function will be measured by 2-D and 3-D echocardiography including Global Longitudinal Strain as described previously.[37] The rate of cardiac dysfunction was approximately 11% in a recent large randomized trial of sunitinib in which schedule 4/2 was utilized.[12] However, to date, testing for cardiac dysfunction in clinical trials has only been performed at rest. We hypothesize that the addition of stress echocardiography will reveal other abnormalities.

Muscle Function will be evaluated by two outcomes: (1) *upper and lower extremity maximal muscular strength* will be assessed as a voluntary one-repetition maximum (1-RM) and muscular endurance (number of repetitions to fatigue at 70% of 1-RM); and (2) *muscle cross-sectional area (CSA) of the major muscles near L3* will be assessed using standard of care restaging computed tomography (CT) scans and Slice-O-Matic software (TomoVision; Magog, Canada), as described previously. Standard-of-care CT scans at baseline and after 12 weeks will be used for the muscle CSA analysis. Sarcopenia, reflected as loss of muscle CSA, is known both to predict toxicity from and to develop on VEGF receptor TKI therapy. Therefore, sarcopenia may contribute to decline in cardiopulmonary function.[38-40]

PHYSICAL FUNCTIONING/FUNCTIONAL CAPACITY

Chair-Stand Test provides a reliable and valid indicator of functional performance of lower body strength in generally active, community-dwelling older adults.[41] Jones et al. examined the test-retest reliability and construct validity of the 30-second chair stand as a measure of lower body strength in 70 adults over 60 years of age (in comparison to a two maximum leg press test). There was a high correlation between chair-stand performance and maximum weight-adjusted, leg-press performance for both men and women (r = .78 and .71, respectively) supporting the criterion-related validity of the chair stand as a measure of lower body strength. Chair-Stand Test performance decreased significantly across age groups in decades - from the 60s to the 70s to the 80s - and was significantly lower for participants reporting low levels of exercise behavior compared to participants reporting higher levels of exercise behavior. To date, the Chair-Stand Test has not been assessed in patients with mRCC. However, this test, in combination with the Timed Get Up and Go and 6MWD, is widely established as the gold standard for assessment of functional performance in older adults and will complement the performance-based primary outcome of cardiopulmonary function (VO_2peak).

Timed Up and Go is field-based test that assesses a person's mobility. Specifically, the TUG measures the time that a person takes to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. This test has been found to be feasible in the majority of older adults.[42] Scores of 10 seconds or less indicate normal mobility, 11 – 20 seconds are within normal limits for frail, elderly, and disabled subjects, and greater than 20 seconds suggests that further examination is required. To indicate normal vs. below-normal performance, a recommended, practical cut-off value for the TUG is 12 seconds.[43] TUG performance decreases with the presence of mobility impairments.[43] To our knowledge, the TUG test has not been assessed in patients with mRCC. This test, in combination with other functional performance measures, is widely established as the gold standard for assessment of functional performance in older adults and will complement the performance-based primary outcome of cardiopulmonary function (VO_{2peak}).

6-Minute Walk Distance (6MWD): Six-minute walk testing (6MWT) is a simple, clinically feasible, and objective assessment of functional capacity that is practical even in severely deconditioned clinical populations (e.g., chronic heart failure, chronic obstructive pulmonary disease (COPD), and organ transplant recipients). 6MWT is a robust predictor of mortality in non-cancer settings;[44-47] only three studies to date have investigated the prognostic importance of 6MWT in the oncology setting.[48,49]

Specifically, Kasymjanova et al. investigated the association between 6MWD and survival in 64 subjects with inoperable non-small cell lung cancer (NSCLC).[48] Relative to <400 m, a 6MWD ≥400 m was associated with a 56% reduction in the risk of death after adjustment for important covariates. Similarly, in recent work among 118 subjects with histologically confirmed metastatic NSCLC, Jones et al. found that compared with subjects achieving a 6MWD <358.5m, the adjusted hazard ratio (HR) for all-cause mortality was 0.61 (95% CI, 0.34 to 1.07) for a 6MWD of 358.5 – 450 m, and 0.48 (95% CI, 0.24 to 0.93) for a 6MWD >450 m.[50] Interestingly, further work by the same group demonstrated that 6MWD was not an independent predictor of prognosis in 243 subjects with grade III/IV recurrent malignant glioma,[49] suggesting that 6MWD may not be an appropriate clinical tool for objectively assessing physical functioning in all cancer populations.

PATIENT REPORTED OUTCOMES END POINTS (FACIT-F, FKSI-19, Godin Leisure Time Exercise Questionnaire)

Sunitinib treatment causes fatigue and worse QOL; however, the changes that occur with sunitinib on schedule 2/1 and 4/2 have not been prospectively described. Therefore, we propose to describe the changes that occur in this setting.

Because fatigue is a patient reported outcome (PRO) of interest, we will evaluate it using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) questionnaire. The FACIT-F measures severity and impact of fatigue on functioning and health-related quality of life (HRQL) experienced in past seven days [Cella, 2002]. It has been used previously to evaluate fatigue with anti-angiogenesis treatments, including assessments for sunitinib [Motzer, 2005; Beaumont, 2006; Motzer, 2013]. The Functional Assessment of Cancer Therapy-Kidney Symptom Index -19 (FKSI-19) is a disease-specific measure that measures disease and

treatment-related symptoms specifically in renal cancer patients [Rosenbloom, 2007; Rosenbloom, 2008; Rao, 2008]. It includes patient self-reports on experience of symptoms in the past seven days such as lack of energy, pain, bone pain, shortness of breath, fatigue, blood in urine, etc. FKSI-19 has been used in a contemporary trial of sunitinib in mRCC.[12] Finally, because it will be important for interpretation of our data to understand activity levels in both arms, we will evaluate leisure time exercise habits with the simple Godin Leisure Time Exercise Questionnaire.

DEPRESSION (HADS)

Depression will be evaluated as described previously using the Hospital Anxiety and Depression Scale (HADS).[51] Fatigue may be difficult to distinguish versus depression in patients with cancer.[52] Understanding the prevalence of depression is necessary to evaluate the FACIT-Fatigue and other related measures because there are high, positive correlations between fatigue and depression.

EXPLORATORY ENDPOINTS

Blood for use in the **plasma angiome multiplex ELISA** will be collected at the same time points as the cardiopulmonary function studies for correlation with primary and secondary endpoints as described previously.[53] Samples will be processed in the Phase I Biomarker Laboratory at Duke (Director: Andrew Nixon, PhD), Molecular Reference Laboratory for the Alliance Oncology Cooperative Group, a national clinical trial research group sponsored by the National Cancer Institute. In cancer patients on therapy, circulating angiogenic factors may be modulated by exercise training during systemic therapy.[54] Therefore, angiogenic biomarker signatures may also predict changes in exercise capacity with therapy.

Changes in Daily Physical Activity will be recorded in a subset of patients (up to 16 total, on either arm) using Bluetooth-enabled fitness trackers (Garmin Ltd) paired with the patients' smartphones. Physical activity will be reported in steps per day. This will allow real-time continuous evaluation of a measure of physical functioning that could be scalable to outpatient oncology clinics. We have shown the feasibility of transferring daily step counts from the patient's device to the investigator through setting up an on-line account with a data transferring service known as Self-Generated Health Information exchange (SGHIx, https://sghix.org) in a previously IRB approved protocol (Duke Pro00063108, unpublished data).

Self-Generated Health Information Exchange (SGHIx) is a web based health information platform (https://app.sghix.org/), developed and managed by Promantus Inc., which specializes in providing a service for patients to set up an account where they can securely integrate their own health data into one platform. Patients can decide who, including their physicians, has access to their own patient generated health data. Access to data can be turned on and off by the patient through this web service. SGHIx was selected as it gives patients the privacy to determine how and when others have access to their patient data.

Changes in Blood Pressure will also be recorded in the same subset of patients using Bluetooth-enabled blood pressure cuffs (iHealth, Inc.) paired with the patients' smartphones. Blood pressure will be reported in mmHg on a daily basis. This will allow real-time continuous evaluation of BP, which is both a pharmacodynamic marker of benefit and a key toxicity that may contribute to declines in VO_2peak. Blood pressure data will also be transferred through SGHIx as detailed in the previous paragraph.

5.6 Definition of Evaluable Subjects

For the primary analysis of change in VO_2peak, patients with measurements at baseline and after 12 weeks are evaluable.

5.7 Early Study Termination

This study can be terminated at any time for any reason by the Duke PI-sponsor. If this occurs, all subjects on study should be notified by the appropriate study personnel as soon as possible. Additional procedures

and/or follow up should occur in accordance with **Section 8.8, Early Withdrawal of Subject(s)**, which describes procedures and process for prematurely withdrawn subjects.

6 STUDY DRUG: SUNITINIB

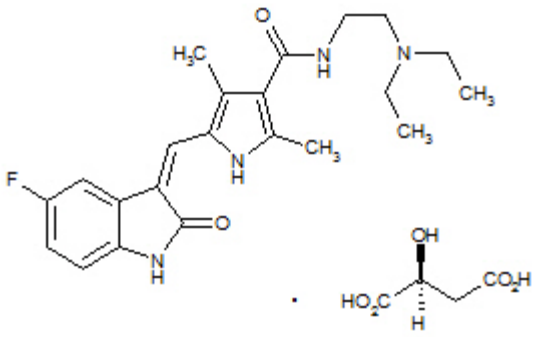
6.1 Names, Classification, and Mechanism of Action

Sunitinib (Sutent®) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony-stimulating factor receptor Type 1 (CSF-1R), and the glial cell line-derived neurotrophic factor receptor (RET).

6.2 Packaging and Labeling

SUTENT, an oral multi-kinase inhibitor, is the malate salt of sunitinib. Sunitinib malate is described chemically as Butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is $C_{22}H_{27}FN_4O_2 \cdot C_4H_6O_5$, and the molecular weight is 532.6 Daltons.

The chemical structure of sunitinib malate is:



Sunitinib malate is a yellow to orange powder with a pKa of 8.95. The solubility of sunitinib malate in aqueous media over the range pH 1.2 to pH 6.8 is in excess of 25 mg/mL. The log of the distribution coefficient (octanol/water) at pH 7 is 5.2.

SUTENT (sunitinib malate) capsules are supplied as printed hard-shell capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg, 37.5 mg, or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate as inactive ingredients.

The orange gelatin capsule shells contain titanium dioxide and red iron oxide. The caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide, and black iron oxide. The yellow gelatin capsule shells contain titanium dioxide and yellow iron oxide. The white printing ink contains shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide. The black printing ink contains shellac, propylene glycol, potassium hydroxide, and black iron oxide.

See the sunitinib package insert for full details:
http://www.labeling.pfizer.com/ShowLabeling.aspx?id=607#S7.1

6.3 Supply, Receipt, and Storage

No study drug (i.e., sunitinib) is being provided by the study. Investigators are responsible for ensuring subjects receive commercially available supplies of sunitinib for the entire duration of study participation.

6.4 Dispensing

Not applicable

6.5 Compliance, Accountability, Reconciliation, and Return

Not applicable

7 SUBJECT ELIGIBILITY

7.1 Inclusion Criteria

1. Age ≥ 18 years.
2. Histologically confirmed renal cell carcinoma (RCC)
3. One of the two following populations:
   a. High risk for recurrence of RCC after nephrectomy, in the opinion of the investigator, *OR*
   b. Locally advanced, unresectable *or* metastatic disease, in the opinion of the investigator, and good or intermediate risk by IDMC Heng Criteria (see **Appendix I**).[4]
4. Karnofsky Performance Status (KPS) ≥ 80 (see **Appendix A**)
5. Appropriate for treatment with sunitinib in the opinion of the treating physician.
6. Able to swallow sunitinib and comply with study requirements.
7. Able to walk and jog on a treadmill, in the opinion of the treating physician.
8. Must be able to complete an acceptable cardiopulmonary exercise test (CPET) at baseline defined as at least one of the following:
   - Achieving a plateau in oxygen consumption concurrent with an increase in power output;
   - Respiratory exchange ratio ≥ 1.1 (RER);
   - Volitional exhaustion with a rating of perceived exertion ≥17 (RPE).
9. Subjects must have normal organ and marrow function as defined below:
   - Absolute neutrophil count ≥1,200/µL
   - Hemoglobin ≥9 g/dL
   - Platelets ≥75,000/µL
   - Total bilirubin ≤1.5 x institutional upper limit of normal
   - AST(SGOT)/ALT(SGPT) <2.5 x institutional upper limit of normal
   - Urine protein creatinine (UPC) ratio of <1 (see **Appendix G** schedule of events footnote)
   - Creatinine ≤2.0 OR creatinine clearance >30 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal (see **Appendix H**).
   - Left ventricular ejection fraction (LVEF) ≥lower limit of institutional normal as assessed by echocardiography.
10. For the sixteen patients who elect to participate in the optional technology portion involving electronic step counts and blood pressure monitoring, the patient must have a Bluetooth-enabled smart phone, which is compatible with the wireless health monitors.
11. For women of childbearing potential (WOCBP) must have a negative serum pregnancy test prior to the start of the study. Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

12. For men who are sexually active, must agree to use a two medically acceptable forms of birth control (one of which must include a condom as a barrier method of contraception) in order to be in this study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. Men must also agree to inform their partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, the subject will need to report it to the study doctor, and she should promptly notify her doctor. The study doctor will ask if the subject's partner is willing to provide updates on the progress of the pregnancy and its outcome. If the subject's partner agrees, this information will be provided to Pfizer, Inc. for safety monitoring follow-up.

7.2 Exclusion Criteria

1. Any prior anti-VEGF therapies (i.e., sunitinib, sorafenib, pazopanib, axitinib, cabozantinib, bevacizumab, etc.), including in the adjuvant or neoadjuvant setting.
2. Prior systemic therapy for *advanced* RCC; however, treatment with immunotherapy (i.e., high-dose bolus IL-2, ipilumumab + nivolumab, etc.) is allowed.
3. Subjects who are receiving any other investigational agents.
4. Subjects who are receiving strong CYP3A4 inhibitors or CYP3A4 inducers (see **Section 5.3.2.2**).
5. Radiotherapy within 2 weeks prior to taking the first dose of study drug, or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
6. Central nervous system (CNS) metastases at baseline, with the exception of those subjects who have previously treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and who meet both of the following criteria: a) are asymptomatic, and b) have no requirement for steroids or enzyme-inducing anticonvulsants in the prior 28 days.
7. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:
   - Active peptic ulcer disease
   - Known intraluminal metastatic lesion(s) with risk of bleeding
   - Inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal conditions with increased risk of perforation
   - History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment
8. History of any one or more of the following cardiovascular conditions within the past 6 months:
   - Cardiac angioplasty or stenting
   - Myocardial infarction
   - Unstable angina
   - Coronary artery bypass graft surgery
   - Symptomatic peripheral vascular disease
   - Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (see **Appendix J**)
9. Absolute contraindications to cardiopulmonary exercise testing and/or aerobic training, as determined by the attending oncologist:
   Absolute Contraindications
   - Uncontrolled arrhythmia causing symptoms or hemodynamic compromise
   - Recurrent syncope
   - Active endocarditis
   - Acute myocarditis or pericarditis
   - Symptomatic severe aortic stenosis

- Uncontrolled heart failure
- Suspected dissecting aneurysm
- Uncontrolled asthma
- Pulmonary edema
- Room air desaturation at rest ≤85%
- Respiratory failure
- Acute non-cardiopulmonary disorders that may affect exercise performance or be aggravated by exercise (i.e., infection, renal failure, thyrotoxicosis)
- Mental impairment leading to inability to cooperate.

10. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of >150 mmHg or diastolic blood pressure (DBP) of >90 mmHg].
11. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism, or untreated deep venous thrombosis (DVT) within the past 6 months.
12. Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement are not considered to be major surgery).
13. Osseous metastatic disease with unacceptable risk of impending fracture due to study assessments, in the opinion of the investigator
14. Evidence of active bleeding or bleeding diathesis.
15. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage.

8 SCREENING, REGISTRATION, AND ON-STUDY TESTS AND PROCEDURES

In addition to assessment for the **primary** endpoint (VO_2peak) by cardiopulmonary exercise testing (CPET), **secondary** and **exploratory** assessments for functional capacity, quantitative skeletal muscle function, patient-reported outcomes, and other endpoints will occur throughout the study as specified in Table 3, Schedule of Events.

The important time periods [and windows] during the study include:

- **Screening** on Day -84 to -1
- **Exercise Testing A [Day -28 to -1]**
- **Exercise Testing B [Day -28 to -1, at least 24 hours before or after the CPET as part of Exercise Testing A]**
- **Randomization on Day -1 [Day -28 to -1], may occur on the same day as Exercise Testing B but after Inclusion/Exclusion criteria have been completed**
- **Treatment Period:** Sunitinib from Day 1 to 85
- **End of Treatment Visit** either 30 days after the last dose of sunitinib or on Day 85, whichever occurs first. (There is no Safety Follow Up Visit in this study because the vast majority of patients are expected to continue sunitinib beyond Day 85 per standard of care.)

All subjects will receive treatment with sunitinib according to the schedule to which they are randomized.

TABLE 3. SCHEDULE OF EVENTS

Phase		Screening	Exercise Testing A[c,d]	Exercise Testing B and Randomization[c]	Treatment Period			End of Treatment Visit	Unscheduled Visit[a]
Day		-84 to -1	-4	-2/-1	1	**4/2:** 29 **2/1:** 36	85	NA	NA
Week		-12 to -1			1	**4/2:** 4 **2/1:** 5	13	See **Note**	NA
Window (Days)		NA	-28 to -1	-28 to -1	NA[d]	±3	±3	±7	NA
General Evaluations	**See Section**								
Informed Consent[b]	8.1.1.1	X							
Eligibility Criteria	7	X							
Medical History	8.9.1	X							
Randomization[c]	8.3			X[c]					
Physical Exam[e]	8.9.2	X	X		X[o]	X	X	X	X
Height, Weight, BMI[n]	8.9.2	X	X		X[o]	X	X	X	X
Vital Signs[f]	8.9.2	X	X		X[o]	X	X	X	X
Performance Status[g]	App. A	X	X		X[o]	X	X	X	X
Concomitant Medications	5.3.2	X	X		X[o]	X	X	X	X
Adverse Events[h]	9.1	X	X	x	X[o]	X	X	X	X
Laboratory Evaluations									
CBC with Platelets	8.1-8.6	X	X		X[o]	X	X	X	X[i]
Serum Chemistry	8.1-8.6	X	X		X[o]	X	X	X	X[i]
Thyroid Function[j]	8.1-8.6	X				X	X		
UPC[k]	App. G	X	X		X[o]	X	X	X	X[i]
Serum Pregnancy Test (WOCBP Only)		X							
Echo	8.1	X							
Disease Evaluations									
CT Chest, Abdomen, Pelvis		X[l]					X		
Bone Scan (opt.)		X[l]							
Objective Evaluations									
CPET	8.9.3		X			X	X		
Rest and Exercise 2-D + 3-D Echo	8.9.3		X				X		
Muscular Strength/Muscular Endurance [m]	8.9.3			X		X	X		
Muscle CSA[l]	8.9.3		X				X		
Chair Stand	8.9.3			X		X	X		
Timed Up and Go	8.9.3			X		X	X		
6 min walk distance	8.9.3			X		X	X		
FACIT-Fatigue	App. B		X			X	X		
FKSI-19	App. C		X			X	X		
Godin Leisure	App. D		X			X	X		

HADS	App. E		X			X	X		
Drug Diary[p]					x	X	X	X	X
Plasma Angiome Multiplex ELISA	8.9.3		X				X		
Step Counts	8.9.3		X			X	X		
Blood Pressure	8.9.3		X			X	X		
Treatment									
Sunitinib 4/2	5.1				X	X	X		
Sunitinib 2/1	5.1				X	X	X		

Note: The End-of-Treatment Visit will occur approximately 30 days after the last dose of sunitinib or on Day 85, whichever occurs first.

a. Unscheduled visits may be performed at any time during the study as clinically indicated to assess for or follow-up on AEs. Unscheduled visits may also occur due to holidays or other scheduling difficulties.
b. Informed consent may be performed within 84 days prior to enrollment (Day 1), but it must be obtained prior to the performance of any study-specific procedures.
c. Randomization should be performed after baseline testing (specifically, CPET) is completed from day -28 to -1, but only after eligibility is confirmed. Note that the Baseline Exercise Testing Visits are structured to take place over 1-2 consecutive days. **See also footnote d. below.**
d. Day 1 is defined as the day the patient begins taking sunitinib. Because day 1 is defined by this activity, there is no window. The day 1 Physical Exam, Weight, BMI, Vital Signs, PS, Con Meds, AEs, and labs have a ±3 day window.
e. A complete physical examination is required at the Screening, Exercise Testing Day A, Day 29-36, and Day 85 visits. A brief symptom-directed physical examination should be performed at all other clinic visits.
f. Vital signs (temperature, blood pressure, heart rate) are to be obtained at each visit. SpO2 collected at baseline.
g. Performance status measured by KPS (as part of IDMC) (see **Appendix A**) at screening. KPS will be used throughout the remainder of the study.
h. All non-serious adverse events will be collected from the time of first dose of study drug until the End of Treatment Visit. Serious adverse events that are related to study procedures are recorded from the time the informed consent form is signed until the End of Treatment Visit (or screen failure). In the event of no End of Treatment Visit, adverse event information will be collected through 30 days after the last dose of study drug. Subjects should be contacted by phone for adverse event follow-up if they do not come to the clinic for the End of Treatment Visit.
i. Clinical laboratory tests may be performed at unscheduled visits if clinically indicated.
j. Thyroid function tests (TFTs) should include TSH and free T4.
k. If UPC ≥1 (see **Appendix G**) at the baseline/ screening assessment, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible.
l. Computed tomography (CT) chest, abdomen, and pelvis should be performed at the time of screening and after 12 weeks (at day 1 of week 13). PET/CT is allowed but should be performed at both timepoints for consistency. Muscle CSA will be calculated from these scans. Scans may be used to calculate Muscle CSA if they were collected within the window for collection of that scan, Bone scan is optional, based on clinical suspicion at baseline.
m. Muscular Strength and Muscular Endurance must be done at least 24 hours before or after CPET to allow adequate recovery time.
n. Height is only required to be collected at screening.
o. Physical Exam, Weight, BMI, Vital Signs, PS, Con Meds, AEs, and labs do not need to be repeated if performed within 14 days of day 1.
p. Drug Diary given to subject on Treatment Day 1. Drug Diary collected on all other visits.

BMI, body mass index; KPS, Karnofsky Performance Status; CBC, complete blood count; CT, computed tomography; opt., optional; CPET, cardiopulmonary exercise test; ; CSA, cross-sectional area; FACIT, Functional Assessment of Chronic Illness Therapy; FKSI-19, Functional Assessment of Cancer Therapy-Kidney Symptom Index-19.

8.1 Screening Examination

The screening examination will take place between Day -84 and -1. The subject must sign an Informed Consent before any screening procedure takes place. Subject data to be collected at the Screening Examination includes:

- Informed Consent
- Eligibility Criteria
- Medical History
- Physical Exam
- Height, Weight, BMI
- Vital Signs
- Performance Status (KPS)
- Concomitant Medications
- Adverse Events (baseline symptoms)

- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Thyroid function (TSH and free T4)
- UPC (see **Appendix G**)
- Serum pregnancy test
- Echo
- CT chest, abdomen, and pelvis
- Bone scan (optional; if subject has known bone metastases then bone scan is required)

8.1.1 Subject Registration

After signing informed consent and completing eligibility screening, subjects who are selected to participate will be registered in the Duke clinical trial subject registry within 1 business day. A record of subjects who fail to meet entry criteria (i.e., screen failures) will be maintained. **Note:** Subject registration must be complete before beginning any treatment.

8.1.1.1 Informed Consent

Authorized study personnel should fully explain the scope of the study to each subject before obtaining informed consent. Subjects should be advised of any known risks inherent in the planned procedures, of any alternative treatment options, of their right to withdraw from the study at any time for any reason, and of their right to privacy.

When obtaining informed consent, study personnel should complete the following steps:

1. Confirm that the subject is a potential candidate for study participation.
2. Obtain dated and signed informed consent.
3. Confirm that the subject is eligible as defined in **Section 7**, Subject Eligibility. A record of subjects who fail to meet entry criteria (i.e., screening failures) will be maintained.

8.1.1.2 Subject Registration

Subject registration for all subjects signing informed consent will be completed by Duke University Medical Center Genitourinary Oncology Group. Following consent and completion of the Eligibility Checklist, documents will be submitted for review and registration of subject. Enrolled subjects will be assigned a unique study ID.

Refer to Subject Registration Instructions (see **Section 8.1.1**) for details.

Subjects will be enrolled only after all pre-treatment screening evaluations are completed and all eligibility criteria are met. When the subject has signed consent and been found to meet all eligibility criteria, the subject will be enrolled, and a unique patient study identification number will be assigned. Treatment must not commence until the subject has received their identification number .

8.2 Exercise Testing Days A and B

An informed consent must be signed by the subject before any screening procedure takes place. Baseline exercise testing will take place between Day -28 and -1, over approximately 2 days (CPET and Muscular Strength must be at least 24 hours apart). Subject data to be collected at Baseline Exercise Testing includes:

Examination and procedures include:

- Physical Exam
- Weight, BMI

- Vital Signs
- Performance Status (KPS)
- Concomitant Medications
- Adverse Events (SAE's)
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO_2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- UPC (see **Appendix G**)
- CPET
- Rest and exercise 2-D and 3-D echocardiography
- Muscular Strength (must be at least 24 hours before or after CPET to allow for adequate recovery)
- Muscular Endurance (must be at least 24 hours before or after CPET to allow for adequate recovery)
- Muscle CSA (CT)
- Chair Stand
- Timed Up and Go
- 6 Minute Walk Distance
- FACIT-Fatigue
- FKSI-19
- Godin Leisure Time Exercise Questionnaire
- HADS
- Plasma angiome multiplex ELISA
- Step counts (give device to subject, optional)
- Blood pressure (give device to subject, optional)

8.3 Randomization

Subjects will be randomized after inclusion/exclusion criteria are met, exercise testing is complete and subject has completed an acceptable CPET and Muscular Strength. Exercise Testing Day B and Randomization may occur on the same day if eligibility is confirmed prior to randomization. Randomization and related activities can occur between days -28 to -1.

8.4 Treatment Period: Day 1

Day 1 is defined as the day on which the subject begins taking sunitinib.
Note: Subjects should start treatment with sunitinib according to the schedule to which they are randomized.

Examinations include:

- Physical Exam
- Weight, BMI
- Vital Signs
- Performance Status (KPS)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO_2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- UPC (see **Appendix G**)
- Note: Many of these activities do not need to be repeated if they are performed within 14 days of day 1 (see **Schedule of Events**).
- Drug diary (give to subject)

8.5 Treatment Period (Schedule 4/2: Day 29; Schedule 2/1: Day 36)

Subject data to be collected includes:

- Physical Exam
- Weight, BMI
- Vital Signs
- Performance Status (KPS)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Thyroid function (TSH and free T4)
- UPC (see **Appendix G**)
- CPET
- Chair Stand
- Timed Up and Go
- 6 Minute Walk Distance
- FACIT-Fatigue
- FKSI-19
- Godin Leisure Time Exercise Questionnaire
- HADS
- Drug diary (collect)
- Step counts (record, optional)
- Blood pressure (record, optional)

Note: Remind subject to re-order sunitinib so that he/she has adequate supply.

8.6 Treatment Period: Day 85

Subject data to be collected includes:

- Physical Exam
- Weight, BMI
- Vital Signs
- Performance Status (KPS)
- Concomitant Medications
- Adverse Events
- CBC with Platelets (hemoglobin, hematocrit, platelet count, white blood cell count, total [absolute] neutrophils)
- Serum Chemistry (sodium, potassium, chloride, total CO2 [bicarbonate], calcium, BUN, creatinine, glucose, albumin, total bilirubin, total protein, alkaline phosphatase, AST, ALT)
- Thyroid function (TSH and free T4)
- UPC (see **Appendix G**)
- CT chest, abdomen, and pelvis
- Bone scan (if ordered at baseline)
- CPET
- Rest and exercise 2-D and 3-D echocardiography
- Muscular Strength (*must be at least 24 hours before or after CPET to allow for adequate recovery*)
- Muscular Endurance (*must be at least 24 hours before or after CPET to allow for adequate recovery*)

- Muscle CSA (CT)
- Chair Stand
- Timed Up and Go
- 6 Minute Walk Distance
- FACIT-Fatigue
- FKSI-19
- Godin Leisure Time Exercise Questionnaire
- HADS
- Drug diary (collect)
- Plasma angiome multiplex ELISA
- Step counts (record, optional)
- Blood pressure (record, optional)

8.7 Off Study and End of Study

The End of Treatment Visit will occur approximately 30 days after the last dose of sunitinib or on Day 85, whichever occurs first. **Note:** There is no Safety Follow Up Visit in this study because the vast majority of patients are expected to continue sunitinib beyond Day 85 per standard of care (see **Table 3. Schedule of Events**).

A subject is considered off study when he/she has completed the End of Treatment Visit. All subjects discontinuing study drug for any reason will have an End Of Treatment Visit approximately 30 days after their last dose of study drug or prior to initiation of cytotoxic or investigational therapy, whichever occurs first.

Reasonable effort should be made to contact any subject lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Such efforts should be documented in the source documents.

The end of the study will occur when the last enrolled subject has completed his/her End of Treatment Visit. A database lock will occur when the data has been cleaned to the specifications in the data quality plan. The database will then be frozen, and no further changes will be permitted.

8.8 Early Withdrawal of Subject(s)

8.8.1 Criteria for Early Withdrawal(s)

Subjects may voluntarily withdraw from the study at any time. The PI may also withdraw a subject from the study at any time based on his/her discretion. Reasons for PI-initiated withdrawal may include, but is not limited to, the following:

- Adverse events
- Abnormal laboratory values
- Abnormal test procedure results
- Protocol deviation
- Administrative issues
- Disease progression, defined as follows:
  - Clinical progression (in the opinion of the investigator)
  - Radiographic progression (in the opinion of the investigator)

8.8.2 Follow-up Requirements for Early Withdrawal(s)

After early withdrawal, the subject must complete the End of Treatment Visit. All subjects discontinuing study drug for any reason will have an End of Treatment Visit approximately (1) 30 days after their last

dose of study drug or (2) prior to initiation of cytotoxic or investigational therapy, whichever occurs first.

8.8.3 Replacement of Early Withdrawal(s)

Subjects who withdraw prior to completing the baseline assessment for the primary endpoint will be replaced. **Note:** See **Section 7.1, Inclusion Criteria**.

8.9 Study Assessments

8.9.1 Medical History

Medical history, such as previous treatments, procedures, and conditions, will be collected during the screening period.

8.9.2 Physical Exam

Evaluations should be performed by the same evaluator throughout the study whenever possible. Weight will be recorded at every visit. Height will be recorded at screening visit only. Body mass index (BMI) will be calculated at every visit. Vital signs include temperature, blood pressure, and heart rate. A complete physical examination is required at the Screening, Day 1, Day 29-37, and Day 85 visits. A brief symptom-directed physical examination should be performed at all other clinic visits.

8.9.3 Evaluations

Cardiopulmonary Exercise Testing (CPET)

Exercise Capacity will be assessed using a symptom-limited CPET on a motorized treadmill with expired gas analysis to determine VO_2peak, according to guidelines for clinical populations.[55] All CPET data will be recorded as the highest 30 second value elicited during the CPET. During exercise, heart rate and rhythm will be monitored continuously using a 12-lead ECG. Equipment with similar technical specifications will be used across the study sites to ensure reasonably accurate and precise results.

Rest and Exercise 2-D and 3-D Echocardiography

Resting left ventricular (LV) function will be assessed by LVEF using 2-dimensional echocardiography (2DE) and 3-dimensional echocardiography (3DE), as well as by global longitudinal strain (GLS) using 2-dimensional speckle-tracking echocardiography (2D-STE) as previously described.[37] After resting assessments, subjects will complete cardiopulmonary exercise testing as above with stress 2DE immediately post-CPET.

Skeletal Muscle Function

Muscle Cross-Sectional Area (CSA) will be assessed using standard-of-care CT scans. Slice-O-Matic (Tomovision, Magog, QC, Canada) software will be used to measure muscle cross-sectional area and adipose tissue (subcutaneous, visceral) cross-sectional area by analysis of axial CT cross-sectional images at the time points described (see **Table 3. Schedule of Events**), as has been done previously.[56] Average muscle and adiposity measurements will be made between 2 separate axial image cuts from each CT scan at the level of L3 by two separate reviewers who will be trained by a radiologist. The major muscles measured near L3 will include the rectus abdominis, latissimus dorsi, external and internal oblique, psoas major, erector spinae, transversospinalis, and quadratus lumborum.

Muscle Strength of the upper and lower body will be assessed as a one-repetition maximum (1-RM). A 1-RM is defined as the greatest resistance that can be moved through the full range of motion in a controlled manner. This dynamic strength assessment will be conducted using the following exercises:

leg press, chest press, and row. The heaviest weight lifted while adhering to the strict technique and form will be used to score the assessment. A certified exercise physiologist or trained designee will conduct this assessment in a controlled environment. Mean percentage of age and sex-predicted muscle strength will be obtained from available normative data.

Muscular Endurance of the upper and lower body will be assessed as the number of repetitions *to* fatigue at 70% of the 1-RM. The same exercises and methods will be used as in the 1-RM determination detailed above. Subjects will continue until technique, tempo, volition, or inability to complete two consecutive repetitions cause finality (per discretion of the exercise physiologist or trained designee).

Physical Functioning/Functional Capacity

Physical Functioning/Functional Capacity will be assessed using the following assessments: Chair-Stand Test, Timed Up and Go, and 6-Minute Walk Distance outcomes as described previously.[57] [41,58,59]These measures will complement the exercise capacity measure.

Chair-Stand Test: The 5-repetition Chair-Stand Test measures the time taken to complete 5 repetitions of the sit-to-stand maneuver. All sit-to-stand maneuvers will be performed from a chair without an arm rest at 43 cm in height and 47.5 cm in depth. Standardized instructions will be provided as follows: "By the count of 3, please stand up and sit down as quickly as possible for 5 times. Place your hands on your lap, and do not use them throughout the procedure. Lean your back against the chair's backrest at the end of every repetition." **Note:** Timing will start when the subject's back left the backrest and will be stopped once the back touched the backrest.

Timed Up and Go: Subjects will be required to stand up from a chair with armrests, walk 3 meters (9.8 feet), turn around, return to the chair, and sit down. **Note:** The time taken to complete this task will be measured in seconds with a stopwatch.[59]

6-Minute Walk Test: The 6-minute Walk Test will be conducted according to the guidelines of the American Thoracic Society (ATS) to determine the 6MWD.[60] Subjects will be instructed to cover the longest distance possible in 6 minutes under the supervision of an exercise physiologist or trained designee. The walked distance will be determined in a measured corridor between 2 cones that were placed 30 meters apart. Age- and sex-predicted 6MWD will be calculated from the equation of Gibbons et al.[61]

Patient-Reported Outcomes

Data on patient-reported changes in fatigue will be collected using the Functional Assessment in Chronic Illness Therapy – Fatigue Questionnaire (**FACIT-F**) that can be found in **Appendix B**. Data on kidney cancer symptoms will be collected using the Functional Assessment of Cancer Therapy-Kidney Symptom Index-19 (**FKSI-19**)that can be found in **Appendix C**. Data on leisure time exercise habits will be collected using the 4-item **Godin Leisure Time Exercise Questionnaire** that can be found in **Appendix D**.[62] Data on depression will be collected using the Hospital Anxiety and Depression Survey (HADS) that can be found in **Appendix E**.

Plasma Angiome Multiplex ELISA

PROCESSING INSTRUCTIONS:

Biomarker assays are time sensitive. Samples must be processed within one hour of collection.

For plasma samples:

1. Draw one 10ml lavender top (K2EDTA) tube (BD Vacutainer, Catalog no. 366643). Please fill the tube completely.
2. Invert tubes 10 times to mix blood
3. Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
4. Remove plasma from tube and transfer equally into two separate clean 15ml polypropylene tubes
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
6. Aliquot approximately 1.0ml of plasma from each tube into each 2.0 ml pink capped cryovial. Total of 5 pink capped cryovials needed for EDTA plasma.
7. Label and freeze at -80°C* (see labeling instructions below)

LABELING INSTRUCTIONS:

Plasma-containing tubes need to be labeled with the following information (label template to be sent electronically):

1. Protocol Name
2. Subject Study Number
3. Subject Initials
4. Sample Date and Time
5. Sample Type (ie. EDTA plasma)

Step Counts and Blood Pressure Monitoring (both optional; up to N=16)

- Subjects in this portion of the study must have Bluetooth-enabled smart phone.
- Each subject who elects to participate in this optional assessment will be provided a Garmin wrist-worn accelerometer and will be taught to download the Garmin smart phone application.
- Subjects will also be provided an iHealth BP cuff that will allow the patient to monitor his or her BP.
- Each subject will be taught by a trained staff member regarding general use of the activity tracker (Garmin Ltd) and wireless BP cuff (iHealth, Inc) to monitor the patient's step and blood pressure respectively. Both the activity monitor and wireless BP cuff are commercially available devices, with easy-to-use instruction manuals. The patient will need to set up an SGHIx account (web-based software platform, developed and managed by Promantus Inc., which will securely transmit device data to the investigator; http://sghix.org). A trained staff member will help the patient set up this account, which will allow the patient to send their activity tracker and blood pressure data electronically directly to the investigators.
- The patients will be recommended to monitor their activity and blood pressure on a daily basis, but the patient will have full autonomy regarding usage of these devices as well as the data they will wish to share with the investigators through the online data transferring website SGHIx.
- All patient health data from SGHIx will be downloaded by the investigators or study personnel and transferred to the study's Medidata RAVE database.

9 SAFETY MONITORING AND REPORTING

The PI is responsible for the identification and documentation of adverse events (AEs) and serious adverse events (SAEs). At each study visit, the PI or trained designee must assess, through non-suggestive inquiries of the subject or evaluation of study assessments, whether an AE or SAE has occurred.

9.1 Adverse Events (AEs)

An adverse event (AE) is any untoward medical occurrence in a subject receiving study drug and that does not necessarily have a causal relationship with this treatment. For this protocol, the definition of AE also includes worsening of any pre-existing medical condition. An AE can therefore be any unfavorable and unintended or worsening sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of sunitinib, whether or not related to use of the sunitinib. Abnormal laboratory findings without clinical significance (based on the PI's judgment) should not be recorded as AEs. **Note:** Laboratory value changes that require therapy or adjustment in prior therapy are considered adverse events.

All non-serious adverse events will be collected from the time of first dose of study drug until the End of Treatment Visit. Serious adverse events that are related to study procedures are recorded from the time the informed consent form is signed until the End of Treatment Visit (or screen failure). These AEs must be recorded in the subject's medical record and adverse events case report form.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or fatal (5).

Attribution of AEs will be indicated as follows:

- Definite: The AE is clearly related to the study drug or exercise testing.
- Probably: The AE is likely related to the study drug or exercise testing.
- Possible: The AE may be related to the study drug or exercise testing.
- Unlikely: The AE is doubtfully related to the study drug or exercise testing.
- Unrelated: The AE is clearly NOT related to the study drug or exercise testing.

9.1.1 AEs of Special Interest

"Fatigue" and "generalized muscle weakness" (regardless of site) are AEs of special interest. Care should be taken to appropriately identify, grade, and note the attribution of these AEs throughout the study. **Note:** There is no special reporting requirement for these AEs.

9.1.2 Expected AEs with Exercise Testing (CPET)

Anticipated (expected) side-effects associated with a symptom-limited cardiopulmonary exercise test include:

- Fatigue
- Muscle soreness
- Joint pain
- Lower back pain
- Leg cramps

Unanticipated but possible side-effects that are rare, but serious include:

- Cardiovascular: angina, AV blocks, bradycardia, edema, hypotension, palpitations, rebound hypertension, shock, syncope
- Arrhythmias
- Myocardial ischemia
- Sudden cardiac death
- Cerebrovascular accident

9.2 Serious Adverse Events (SAEs)

An AE is considered "serious" if in the opinion of the investigator it is one of the following outcomes:

- Fatal
- Life threatening
- Constitutes a congenital anomaly or birth defect
- A medically significant condition (defined as an event that compromises subject safety or may require medical or surgical intervention to prevent one of the three outcomes above).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption to conduct normal life functions

SAE reporting criteria defined below

A. **Subset of SAEs Reportable for this Study.** Because the Pfizer Product used in this Study is a mature marketed product with a well-established safety profile, only SAEs that fit into any of the following categories need to be reported to Pfizer: (1) a death, regardless of whether it is considered related to treatment with the Pfizer Product, (2) a non-fatal SAE that occurs during the reporting period and that is assessed by the Principal Investigator as both related to treatment with the Pfizer Product and unexpected for that Product, (3) an SAE assessed by the Principal Investigator as related to the Pfizer Product that occurs after the SAE reporting period, or (4) an otherwise reportable event as described in paragraph B., below. An event should be considered "related" to the Pfizer Product if a relationship is at least a reasonable possibility, and "unexpectedness" should be based upon a single safety reference document identified by the Principal Investigator and documented in association with the study.

B. **Exposure During Pregnancy, Exposure During Lactation, Occupational Exposure, and Lack Of Effect**. Even though there may not be an associated SAE, exposure to the Pfizer Product during pregnancy, exposure to the Pfizer Product during lactation, and occupational exposure to the Pfizer Product are reportable, and lack of effect of the Pfizer Product may also be reportable.

9.2.1 Reporting of SAEs

Serious adverse events, whether or not considered drug related, should be reported within 24 hours of becoming aware of the event, using the provided DCI SAE Report Form and the SAE Report Review Form (Site Assessment). These documents should be sent to:

- **The DCI Safety Desk – fax: (919) 681-9357; phone: (919) 681-9538; email: dcccsafe@dm.duke.edu**

Note: If the DCI Safety Desk cannot be reached within 24 hours, the Principal Investigator should be contacted:

- Dr. Michael Harrison, phone: (919) 668-4615; pager: (919) 684-8111; email: michael.harrison@duke.edu

The initial report for each SAE or death should include at minimum the following information:

- Protocol # and title
- Patient initials, study identification number, sex, age
- Date the event occurred
- Description of the SAE
- Dose level and cycle number at the time the SAE occurred
- Description of the patient's condition
- Indication whether the patient remains on study

- Causality

Follow-up information including severity, action taken, concomitant medications, and outcome should be communicated to Duke as soon as possible.

Upon receipt of the DCI SAE Report form by the DCI Safety Desk, the PI will be notified and be required to complete the PI assessment of the DCI SAE Report Review Form. The DCI Safety Desk will, in turn, report the event to Pfizer if the SAE is felt to be at least possibly related to sunitinib using the DCI SAE Report Form. The *Reportable Event Fax Cover Sheet* provided by Pfizer must also be included with each SAE submitted.

The SAE documentation, including the DCI SAE Report Form and available source records, should be faxed to Pfizer per the instructions on the SAE cover sheet.

The following minimum information is required for this documentation and report:

- Study number/IIT regulatory identifier
- Subject number, sex, and age
- Report date
- SAE description (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

Fax and Phone numbers to report SAEs to Pfizer:

Fax: Toll-Free (local): 1 866 997-8322
(Clinical Trial, Compassionate Use , IIR reports)
Tel: 800 752-9737 (toll-free)
ONLY for technical support if fax number is not working

9.3 Procedure in Case of Pregnancy

Sunitinib is Pregnancy Category D.

Sunitinib can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of sunitinib should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic.

Subjects receiving sunitinib are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) starting at the time of screening and continuing throughout the course of treatment and for at least three months after sunitinib is discontinued.

If, during the conduct of the clinical trial, a male subject impregnates his partner, OR a female subject becomes pregnant, the subject should report the pregnancy to the Investigator. With the permission of the pregnant partner, the Investigator should report the pregnancy to Pfizer as an SAE within 24 hours of awareness of the event. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated fertility date, pregnancy result, and neonatal data, etc., should be included in this information.

With the permission of the pregnant partner, the Investigator should report the outcome of the pregnancy (independent of outcome, e.g., full-term delivery, pre-term delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly [including anomaly in a miscarried fetus, etc.]) in accordance with the same reporting procedure as for SAEs (see **Section 9.2.1**). The date of outcome of the pregnancy,

gestational age, date of birth, and neonatal data, etc., should be included in this information. Informed consent will need to be obtained from the pregnant partner to document her permission to disclose this information to Pfizer.

9.4 Safety Oversight Committee (SOC)

The Duke Cancer Institute SOC is responsible for annual data and safety monitoring of DUHS sponsor-investigator Phase I and II, therapeutic interventional studies that do not have an independent Data Safety Monitoring Board (DSMB). The primary focus of the SOC is review of safety data, toxicities, and new information that may affect subject safety or efficacy. Annual safety reviews include, but may not be limited to, review of safety data, enrollment status, stopping rules if applicable, accrual, toxicities, reference literature, and interim analyses as provided by the sponsor-investigator. The SOC in concert with the DCI Monitoring Team (see **Section 10.1** for Monitoring Team description) oversees the conduct of DUHS cancer-related, sponsor-investigator therapeutic intervention and prevention intervention studies that do not have an external monitoring plan, ensuring subject safety and that the protocol is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP), and applicable regulatory requirements.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 DCI Monitoring Team

The Duke Cancer Institute (DCI) Monitoring Team will conduct monitoring visits to ensure subject safety and that the protocol is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, good clinical practice, and applicable regulatory requirements. As specified in the DCI Data and Safety Monitoring Plan, the DCI Monitoring Team will conduct routine monitoring after the third subject is enrolled, followed by annual monitoring of 1 – 3 subjects until the study is closed to enrollment and subjects are no longer receiving study interventions that are more than minimal risk.

Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns and may be initiated upon request of DUHS and DCI leadership, the DCI Cancer Protocol Committee, Duke Clinical Trials Quality Assurance (CTQA), the Safety Oversight Committee (SOC), the Sponsor-Investigator, the site's Principal Investigator, or the IRB. All study documents must be made available upon request to the DCI Monitoring Team and other authorized regulatory authorities, including, but not limited to, the National Institute of Health, National Cancer Institute, and the FDA. Every reasonable effort will be made to maintain confidentiality during study monitoring.

10.2 Data Management and Processing

10.2.1 Study Documentation

Study documentation includes, but is not limited to, source documents, case report forms, monitoring logs, appointment schedules, study team correspondence with sponsors or regulatory bodies/committees, and regulatory documents that can be found in the DCI-mandated "Regulatory Binder" that includes, but is not limited to, signed protocol and amendments, approved and signed informed consent forms, FDA Form 1572, CAP and CLIA laboratory certifications, and clinical supplies receipts and distribution records.

Source documents are original records that contain source data that is all information in original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the

laboratories, and at medico-technical departments involved in the clinical trial. When possible, the original record should be retained as the source document. However, a photocopy is acceptable provided that it is a clear, legible, and an exact duplication of the original document.

10.2.2 Case Report Forms (CRFs)

The electronic CRF will be the primary data collection document for the study and will be updated in a timely manner following acquisition of new source data. Only the research staff members listed on the delegation of authority log are permitted to make entries, changes, or corrections in the CRF.

An audit trail will be maintained automatically by the electronic CRF management system (eCRF). All users of this system will complete user training, as required or appropriate per regulations.

10.2.3 Data Management Procedures and Data Verification

Completeness of entered data will be checked automatically by the eCRF system, and users will be alerted to the presence of data inconsistencies. Additionally, queries may be issued by the study data manager or project leader. Missing or implausible data will be queried for completion or correction (i.e., confirmation of data, correction of data, and completion or confirmation that data is not available, etc.).

The database will be reviewed and discussed prior to database closure, and will be closed only after resolution of all remaining queries. An audit trail will be kept of all subsequent changes to the data.

10.2.4 Study Closure

Following completion of the studies, the PI will be responsible for ensuring the following activities:

- Data clarification and/or resolution
- Accounting, reconciliation, and destruction/return of used and unused study drugs
- Review of site study records for completeness
- Shipment of all remaining laboratory samples to the designated laboratories (i.e., Nixon Lab at Duke)

11 STATISTICAL METHODS AND DATA ANALYSIS

All statistical analysis will be performed under the direction of the statistician designated in key personnel. Any data analysis carried out independently by the investigator must be approved by the statistician before publication or presentation.

11.1 Analysis Sets

The intent-to-treat (ITT) population will consist of all randomized patients. The modified intent-to-treat (ITT) population will consist of all randomized patients who have both a baseline and after week 12 evaluation. In the ITT analyses and the modified ITT analyses patients will be analyzed according to the study arm to which they were randomized. The modified ITT population will be the primary analysis population.

The per-protocol population will consist of all randomized patients with both baseline and after week 12 measurements for the primary endpoint and prior to any analysis: have been deemed compliant and properly evaluated for efficacy per investigator, satisfied all inclusion and exclusion criteria, and correctly assigned treatment.

The safety population will be all patients with at least one safety evaluation.

11.2 Subject Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be summarized for the ITT population. Mean, median, standard deviation, minimum, and maximum will be displayed by treatment arm for continuous variables. Categorical variables will be summarized by counts and percentages for each arm.

11.3 Treatments

Compliance with sunitinib will be described, for each treatment arm, by the number and percent of intended doses taken (dose intensity). Deviations from the planned sunitinib schedule (i.e., 4/2 vs. 2/1) will be presented by numbers and percent of patients. In addition, the number and percent of patients having delays or dose reductions will be displayed by treatment arm.

Numbers of patients discontinuing treatment and reasons for discontinuation will be displayed for each treatment arm. Numbers of patients failing to complete full follow-up (through week 12) and reasons for loss to follow-up will be displayed for each treatment arm.

11.4 Primary Objective

The primary objective is to estimate the change in VO_2peak at after 12 weeks from baseline in treatment-naïve mRCC patients treated with sunitinib on schedules 4/2 and 2/1 separately.

11.4.1 Variable

The primary endpoint is the change in peak oxygen uptake (ΔVO_2peak) from week 1 to through week 12 in each group.

11.4.2 Statistical Hypothesis, Model, and Method of Analysis

The primary analysis will be checking if there is a significant change in peak oxygen uptake (VO_2 peak) from baseline to through week 12 for each schedule, using a paired t-test. The primary analysis will be done for complete cases, (i.e., patients with VO_2peak measured at baseline and after week 12) in the ITT population.

11.5 Secondary and Exploratory Objectives

For subjects with VO_2 peak measures at week 4 or week 5, descriptive statistics including mean, standard deviation, minimum and maximum of VO_2peak changes from baseline to week 4 and to week 5 will also be reported to assess early effects of each sunitinib schedule. Descriptive statistics for other secondary and exploratory endpoints will also be reported for each sunitinib schedule.

In addition, a random effects model will be used to assess the effect of different sunitinib schedules on the VO_2 peak change. In the model repeated measurements of VO_2 peak change at week 4, 5 and through week 12 from baseline are outcomes, schedule indicator (0 for schedule 4/2, 1 for schedule 2/1) is chosen as the main factor, baseline VO_2 peak value and patient characteristics are other included covariates. Similarly, random effects models with other continuous repeated measures (i.e., resting and stress cardiac function and muscle strength) as dependent variables will also be used to analyze the schedule effects.

Sensitivity analyses will be performed for the primary endpoint and key secondary endpoint using Last Value Carried Forward (LOCF) methods. The intent of this sensitivity analysis is to assay the robustness of results observed in the modified ITT population.

Eligibility rate, acceptance rate and adverse event rate will be reported descriptively.

Eligibility rate is defined as the number of subjects eligible for the study divided by the number approached for the study (i.e., screen fail rate).

Acceptance rate is defined as the number of patients agreeing to participate divided by total number randomized.

Rates of adverse events, classified by CTCAE v4.0, will be displayed by body system and preferred term for each arm.

For analysis of the plasma angiome multiplex ELISA data, correlations among analytes will be evaluated by Spearman analysis. Analyte levels at baseline and changes on-treatment will be correlated with baseline VO_2peak and changes in VO_2peak, respectively.

Descriptive statistics and graphical reporting of group and individual patient data will be used to report changes in step counts and blood pressure over time (daily monitoring). We will also determine if there is any association between steps/day and measurements of VO_2peak and association between steps/day and blood pressure measurements of VO_2peak.

11.6 Sample Size Calculation

The primary purpose of this study is to check if changes in cardiopulmonary function (VO_2peak) in patients from baseline to through week 12 is significant for each sunitinib schedules.

This is a pilot study in which 15 evaluable patients per arm will be randomized with equal probability to either the sunitinib 4/2 or 2/1 schedule. The estimated variance based on a previous pilot study is 3.2 (Lee W. Jones, PhD; unpublished data).

Assuming 1) the same variance at baseline and 12 weeks, and 2) no correlation between the two VO_2peak measurements at baseline and 12 weeks, based on 2-sided, paired t-test with 15 patients, the VO_2peak mean difference of 2.0 ml kg^{-1} min^{-1} from baseline to after 12 weeks can be detected with 80% power and significance level 0.05. If we assume a correlation of 0.20 between the two VO_2peak measurements, then the VO_2peak mean difference of 1.8 ml kg^{-1} min^{-1} from baseline to after 12 weeks can be detected. **Note:** Because VO_2peak typically declines by only about 1% per year in adults, this magnitude of decline is believed to be clinically significant.

Because 1) the primary endpoint is mean difference in VO_2peak at after 12 weeks) 30 total patients are required for adequate evaluation, patients who are not able to undergo CPET for determination of VO_2peak at after 12 weeks will be replaced. We estimate a 20% dropout rate so that 36 patients will need to be accrued in order to have 30 total evaluable patients (15 evaluable in each arm).

12 ADMINISTRATIVE AND ETHICAL CONSIDERATIONS

12.1 Regulatory and Ethical Compliance

This protocol was designed and will be conducted and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable federal, state, and local regulations.

12.2 DUHS Institutional Review Board and DCI Cancer Protocol Committee

The protocol, informed consent form, advertising material, and additional protocol-related documents must be submitted to the DUHS Institutional Review Board (IRB) and DCI Cancer Protocol Committee (CPC) for review. The study may be initiated only after the Principal Investigator has received written and dated approval from the CPC and IRB.

The Principal Investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent form. The CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e., amendments affecting subject population, inclusion/exclusion criteria, agent administration, statistical analysis, etc.).

The Principal Investigator must obtain protocol re-approval from the IRB within 1 year of the most recent IRB approval. The Principal Investigator must also obtain protocol re-approval from the CPC within 1 year of the most recent IRB approval, for as long as the protocol remains open to subject enrollment.

12.3 Informed Consent

The informed consent form must be written in a manner that is understandable to the subject population. Prior to its use, the informed consent form must be approved by the IRB.

The Principal Investigator or authorized key personnel will discuss with the potential subject the purpose of the research, methods, potential risks and benefits, subject concerns, and other study-related matters. This discussion will occur in a location that ensures subject privacy and in a manner that minimizes the possibility of coercion. Appropriate accommodations will be made available for potential subjects who cannot read or understand English or are visually impaired. Potential subjects will have the opportunity to contact the Principal investigator or authorized key personnel with questions, and will be given as much time as needed to make an informed decision about participation in the study.

Before conducting any study-specific procedures, the Principal Investigator must obtain written informed consent from the subject or a legally acceptable representative. The original informed consent form will be stored with the subject's study records, and a copy of the informed consent form will be provided to the subject.

12.4 Privacy, Confidentiality, and Data Storage

The Principal Investigator will ensure that subject privacy and confidentiality of the subject's data will be maintained. Research Data Security Plans (RDSPs) will be approved by the appropriate Duke clinical research unit for the Duke site.

To protect privacy, every reasonable effort will be made to prevent undue access to subjects during the course of the study. Prospective participants will be consented in an exam room where it is just the research staff, the patient and his family, if desired. For all future visits, interactions with research staff (study doctor and study coordinators) regarding research activities will take place in a private exam room. All research related interactions with the participant will be conducted by qualified research staff who are directly involved in the conduct of the research study.

To protect confidentiality, subject files in paper format will be stored in secure cabinets under lock and key accessible only by the research staff. Electronic records of subject data will be maintained using a dedicated database which is housed in an encrypted and password-protected DCI file server. Access to electronic databases will be limited to delegated personnel. The security and viability of the IT infrastructure will be managed by the DCI and/or Duke Medicine.

Upon completion of the study, research records will be archived and handled per DUHS HRPP policy. Subject names or identifiers will not be used in reports, presentations at scientific meetings, or publications in scientific journals.

12.5 Data and Safety Monitoring

Data and Safety Monitoring will be performed in accordance with the DCI Data and Safety Monitoring Plan. For a more detailed description of the DSMP for this protocol, refer to the DSMP document.

12.6 Protocol Amendments

All protocol amendments must be initiated by the Principal Investigator and approved by the IRB prior to implementation. IRB approval is not required for protocol changes that occur to protect the safety of a subject from an immediate hazard. However, the Principal Investigator must inform the IRB and all other applicable regulatory agencies of such action immediately.

Though not yet required, the CPC should be informed about any protocol amendments that potentially affect research design or data analysis (i.e., amendments affecting subject population, inclusion/exclusion criteria, agent administration, etc.).

12.7 Records Retention

The Principal Investigator will maintain study-related records at least six years after study completion.

12.8 Conflict of Interest

The Principal Investigator and Sub-Investigators must comply with applicable federal, state, and local regulations regarding reporting and disclosure of conflict of interest. Conflicts of interest may arise from situations in which financial or other personal considerations have the potential to compromise or bias professional judgment and objectivity. Conflicts of interest include but are not limited to royalty or consulting fees, speaking honoraria, advisory board appointments, publicly-traded or privately-held equities, stock options, intellectual property, and gifts.

The Duke University School of Medicine's Research Integrity Office (RIO) reviews and manages research-related conflicts of interest. The Principal Investigator and Sub-Investigators must report conflicts of interest annually and within 10 days of a change in status, and when applicable, must have a documented management plan that is developed in conjunction with the Duke RIO and approved by the IRB/IEC.

13 APPENDICES

Appendix A Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix B FACIT Fatigue Scale (version 4)

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 <u>past 7 days</u>.

	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>.

	<u>EMOTIONAL WELL-BEING</u>	**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

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

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4

An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix C FKSI-19

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.**

		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
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4

DRS-P

	RCC2	I have had blood in my urine	0	1	2	3	4
	C6	I have a good appetite	0	1	2	3	4
DRS-E	GF5	I am sleeping well	0	1	2	3	4
	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
TSE	C5	I have diarrhea (diarrhoea)	0	1	2	3	4
	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	GF1	I am able to work (include work at home)	0	1	2	3	4
FWB	GF3	I am able to enjoy life	0	1	2	3	4
	GF7	I am content with the quality of my life right now	0	1	2	3	4

Appendix D Godin Leisure Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times Per Week	Average Duration (mins)
a) STRENUOUS EXERCISE (HEART BEATS RAPIDLY) (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____	_____
MODERATE EXERCISE (NOT EXHAUSTING) (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____	_____
b) MILD EXERCISE (MINIMAL EFFORT) (e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)	_____	_____

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

OFTEN	SOMETIMES	NEVER/RARELY
1. ☐	2. ☐	3. ☐

APPENDIX E HADS

Instructions: Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he or she will be able to help you more. This questionnaire is designed to help your doctor know how you feel. Read each item and circle the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

APPENDIX F Recommendations for Management of Hypertension

The pathogenesis of hypertension induced by angiogenesis inhibitors is likely to be multi-factorial. VEGF and VEGFR-2 are involved in the proper maintenance, differentiation, and function of endothelial cells. Arterial hypertension is characterized by reduced nitric oxide (NO) biosynthesis, activation of the renin-angiotensin-aldosterone system (RAAS), increased vasoconstriction, and microvascular rarefaction of arterioles and capillaries. Microvascular rarefaction in hypertension is partly due to impaired angiogenesis. Hypertension observed with anti-angiogenic agents is thought to be due to decreased bioavailability of endothelium-derived NO, which is a potent vasodilator, as a result of reduced endothelium function by anti-angiogenesis.

A. Control of Hypertension Prior to Study Entry

For subjects presenting with hypertension, their blood pressure (BP) must be adequately controlled to <150/90 mmHg prior to the first dose of study medication. This can be achieved by adjusting the existing anti-hypertensive medications or adding new one (see below for permitted anti-hypertensive medications).

B. Control of Hypertension during Study Treatment

In event hypertension is worsened or emerged during study treatment; the management of hypertension should include two parts:

1. Dose modification of study medication, including interruption, reduction, re-challenge, or discontinuation of study medication (see **Table 1** for guidelines and algorithm)
2. Management of hypertension with anti-hypertensive medications

The following antihypertensive medications are permitted by the protocol but should be used with caution:

- Dihydropyridine calcium channel blockers: felodipine, nifedipine, nicardipine, nimodipine, nitrendipine, amlodipine, nisoldipine, and isradipine
- Angiotensin II blockers: losartan and irbesartan
- Beta-blockers: carvedilol, metoprolol, propafenone, propranolol, and timolol
- Non-dihydropyridine calcium channel blockers: diltiazem and verapamil

Based on consensus of experts in the field, we recommend the use of dihydropyridine calcium channel blockers (e.g., amlodipine) and ACE inhibitors (e.g., lisinopril) as the first line and second line of therapy, respectively, for treatment-related hypertension. The use of non-dihydropyridine calcium channel blockers diltiazem and verapamil are not encouraged.

The Duke PI should be contacted if there is any concern or need for clarification.

APPENDIX G Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

There is a good correlation between the ratio of urine protein to creatinine concentrations in a random urine sample and the amount of protein excreted in a 24-hour urine collection period. The creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate:

- Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day
- Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day
- Normal protein excretion is <100 mg to 150 mg/24 hours
- The UPC ratio is roughly equal to the 24-hour urine protein excretion in g/day

Calculating (UPC)

UPC ratio = (Urine protein mg/dl) / (urine creatinine mg/dl) = numerically equivalent to gm protein excreted in urine over 24 hours

- Example: Patient has a urine protein = 90 mg/dl and urine creatinine = 30 mg/dl. UPC ratio= (90 mg/dl) / (30 mg/dl) = 3
- Result UPC is 3 (correlates to roughly 3 grams protein excretion in a 24-hour period)

Units for UPC Ratio

Note: Both the protein concentration and the creatinine concentration must be expressed in the same units (mg/dL or g/L) to perform the UPC calculation. (Units will cancel out, such as protein mg/creatinine mg or as protein gm/creatinine gm)

If protein was expressed in mg/dL and creatinine expressed in µmol/L, the UPC ratio would be in mg/µmol, thus, conversion of the units is required (see below):

From	To	Conversion Factor
Conventional Units: mg/dl	SI Units: µmol/l	Multiply by 88.4
SI Units: µmol/l	Conventional Units: mg/dl	Divide by 88.4

Reference:
Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

APPENDIX H COCKCROFT AND GAULT FORMULA FOR ESTIMATED CREATININE CLEARANCE (CrCl)

For US Units:

Cockcroft-Gault CrCl for males (mL/min) = [(140 - age) * (Weight in kg[1])] / (72 * Cr)

Cockcroft-Gault CrCl for females (mL/min) = [(140 - age) * (Weight in kg[1]) * (0.85)] / (72 * Cr)

1. If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimate CrCl.

APPENDIX I IDMC (Heng) Criteria[4]

Step 1: Calculate number of risk factors:

Risk Factor	
KPS	<80%
Time from diagnosis to treatment	<12 months
Hemoglobin	<LLN
Corrected serum calcium*	>ULN
Neutrophil count	>ULN
Platelet count	>ULN

KPS = Karnofsky Performance Status
LLN = lower limit of normal laboratory reference range
ULN = upper limit of normal laboratory reference range

*Corrected calcium (mg/dL) = measured total calcium (mg/dL) + [0.8 (4.0 - serum albumin [g/dL])], where 4.0 represents the average albumin level in g/dL

Step 2: Determine risk status:

Number of Risk Factors	Risk Status
0	Favorable (Good)
1-2	Intermediate
≥3	Poor

APPENDIX J New York Heart Association (NYHA) Classification of Congestive Heart Failure

Class I	Subjects with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Subjects with marked limitation of activity; they are comfortable only at rest.
Class IV	Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

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