Alternating Targeted Therapy in Patients with Metastatic Renal Cell Carcinoma: A Phase II Study of Alternating Sunitinib and Temsirolimus

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1. TITLE: DMS 1011:

Alternating Targeted Therapy in Patients with Metastatic Renal Cell Carcinoma: A Phase II Study of Alternating Sunitinib and Temsirolimus

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Lay Abstract:

In the past 5 years, treatment for metastatic Renal Cell Carcinoma (mRCC) has focused on agents directed at blocking tumor and vascular growth pathways. Sunitinib blocks the vascular endothelial growth factor receptor (VEGFr) and temsirolimus is an inhibitor of mammailian target of rapamycin (mTOR). Both suntinib and temsirolimus are FDA approved agents for mRCC. When agents like these are given together, the toxicity increases but they can be given safely, at full doses, sequentially. We hypothesize that alternating these agents will double the progression free survival (PFS) of the agents when given sequentially. We propose a single arm phase II study to evaluate this.

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3.0 SUMMARY: Alternating Targeted Therapy in Patients with Metastatic Renal Cell Carcinoma: A Phase II Study of Alternating Sunitinib and Temsirolimus

Patients with measurable metastatic renal cell carcinoma (any histology) are eligible. All patients will be treated as outlined below with sunitinib alternating with temsirolimus.

Patients will be treated continuously, until evidence of disease progression, or for up to two cycles following disappearance of all disease. There are not a specified number of cycles a patient may receive while on study.

A cycle is defined as:
Sunitinib 50mg by mouth daily for 4 weeks followed by a two week rest
Temsirolimus 25mg IV weekly for 4 weeks followed by a two week rest

4.0 OBJECTIVES:

4.1 Primary Objectives

4.1.1. To determine the time to progression in metastatic renal cell carcinoma patients treated with alternating targeted therapy.

4.2 Secondary Objectives

4.2.1. To determine the clinical response rate.

4.2.2. To characterize the toxicity profile and quality of life.

5.0 BACKROUND AND RATIONALE

Alternating non-overlapping anticancer therapy was first proposed by Goldie and Coleman as a method to overcome tumor drug resistance (1). This hypothesis was modified to the "worst drug rule" by Day (2). While initial clinical trials employing alternating therapies following Goldie Coleman hypothesis were not always able to confirm the utility of this approach, subsequent studies supported the approach employing the Day hypothesis (3, 4, and 5).

Anti-angiogenesis therapies have recently made significant impact in the care of patients with metastatic renal cell carcinoma (6, 7). There are now 6 targeted anti-angiogenesis agents approved by the US FDA for treatment of metastatic renal cell cancer: sunitinib, sorafenib, pazopanib, bevacizumab (+ interferon alpfa), temsirolimus and everolimus (7). Median time to progression for these agents is from 4-11 months. Although these agents are directed at similar targets, clinical observations support their sequential use. Attempts to combine them have led to increasing toxicity. Interestingly, in a laboratory mouse model, renal tumors which become resistant to sunitinib become sensitive when rested and transferred to syngeneic mice suggesting that resistance may be reversible (8).

Sunitinib is primarily a VEGFR tyrosine kinase inhibitor though it also hits other targets such as PDGF and cKit. It is typically the first line of therapy due to its objective response rate of 40% and a median time to progression of 11 months. The major barrier to its chronic use has been toxicity including hypertension, fatigue, and diarrhea (9). Temsirolimus targets mTOR, a different pathway. While the

objective response is small (<10%), time to progression in the poor risk group is 4 months. It is better tolerated on the whole than sunitinib (10). Combination of temsirolimus with sunitinib leads to worsening toxicity (11). A historical study using temsirolimus after sunitinib failure suggests feasibility and no unexpected side effects which is typically observed in clinical practice as well (12). We hypothesize that alternating sunitinib and temsirolimus therapy will be well tolerated and improve the combined median time to progression of the agents alone (11 + 4 months) by 100% (30 months).

6.0 Eligibility

6.1 Inclusion Criteria

Histologically confirmed metastatic renal cell cancer with evaluable disease.

Patients must be at least 2 weeks from their last immunotherapy, surgery or chemotherapy (6 weeks for nitrosureas) and recovered from all adverse side effects

6.1.iii. Karnofsky Performance Status ≥60%

6.1.iv. Life expectancy ≥ twelve weeks

6.1.v. Adequate end organ function:

Hematologic:

- Absolute neutrophil count (ANC) ≥1.5 X 10^9/L
- Hemoglobin ≥9 g/dL (Subjects may not have had a transfusion within 7 days of screening assessment.)
- Platelets ≥100 X 10^9/L

Hepatic:

- Total bilirubin ≤1.5 X ULN
- AST and ALT ≤2.5 X ULN

(Subjects with Gilbert's Syndrome are eligible if their total bilirubin is <3.0 X ULN and direct bilirubin is < 35%)

Renal:

- Calculated creatinine clearance ≥30 mL/min

Endocrine:

- Total serum calcium concentration <12.0mg/dL

6.1.vi. Women should not be lactating and, if of childbearing age, have a negative pregnancy test within two weeks of entry to the study and practicing acceptable forms of birth control

6.1.vii. Appropriate contraception in both sexes

6.1.viii. The patient must be competent and sign the informed consent.

6.2 EXCLUSION CRITERIA

6.2.i. Concomitant second malignancy except for non-melanoma skin cancer, and non–invasive cancer such as cervical CIS, superficial bladder cancer without local recurrence, breast CIS.

6.2.ii. In patients with a prior history of invasive malignancy, less than five years in complete remission.

6.2.iii. Have evidence of significant co-morbid illness such as uncontrolled diabetes, hypertension or active infection that would preclude treatment on this regimen.

6.2.v. Prior treatment with either sunitinib or temsirolimus

6.2.vi. Clinically significant gastrointestinal abnormalities including, but not limited to:

a. Malabsorption syndrome
b. Major resection of the stomach or small bowel that could affect the absorption of study drug
c. Active peptic ulcer disease
d. Known intraluminal metastatic lesion/s with suspected bleeding
e. Inflammatory bowel disease
f. Ulcerative colitis, or other gastrointestinal conditions with increased risk of perforation
g. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment.

6.2.vii. Presence of uncontrolled infection.

6.2.viii. Prolongation of corrected QT interval (QTc) > 480 milliseconds (msecs).

`````6.2.ix. History of any one or more of the following cardiovascular conditions within the past 12 months:

a. Cardiac angioplasty or stenting
b. Myocardial infarction
c. Unstable angina
d. Coronary artery by-pass graft surgery
e. Symptomatic peripheral vascular disease
f. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)

6.2.x. History of cerebrovascular accident (CVA) including transient ischemic attack (TIA) within the past 12 months.

6.2.xi. History of pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Note: Subjects with recent DVT who have been treated with therapeutic anticoagulating agents for at least 6 weeks are eligible.
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6.2.xii. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥159mmHg or diastolic blood pressure (DBP) of ≥ 99mmHg (17)]. Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry.

6.2.xiii. Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer.

6.2.xiv. Evidence of active bleeding or bleeding diathesis

6.2.xv. Hemoptysis within 6 weeks of first dose of study drug.

6.2.xvi. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels (Note: tumor abutting the vessels is acceptable, but contiguous tumor and vessels are not; CT with contrast is strongly recommended to evaluate such lesions).

6.2.xvii. Any serious and/or unstable pre-existing medical, psychiatric, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study.

6.2.xviii. Is now undergoing and/or has undergone in the 14 days immediately prior to first dose of study drug any minor surgeries (i.e. skin biopsy, tooth extraction, etc.) and recovered from all ill effects.

6.2.xix. Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity.

6.2.xx. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to sunitinib or temsirolimus.

6.2.xxi. Untreated brain metastasis. (Brain metastases that are stable based on radiographic evidence 4 weeks after radiation and/or surgery are permitted).

7.0 Visit Procedures

All patients considered for entry in the trial should have measurable disease as described in the RECIST 1.1 criteria (see appendix). Staging will include:

7.1 Within 4 weeks of Cycle 1 Day 1 (dose 1 of Sunitinib) the following procedures are required:

- 7.1.i CT scans of the chest/abdomen/pelvis
- 7.1.ii Brain MRI or enhanced brain CT.
- 7.1.iv Electrocardiogram (EKG)

7.2 Within 2 weeks of Cycle 1 Day 1 (first dose of Sunitinib) the following procedures are required:

- 7.1.i History assessment and Physical examination

7.1.ii Laboratory tests including:

- Pregnancy test when indicated (urine or serum),
- Complete blood count with differential (CBC w/diff)
- Comprehensive metabolic panel (CMP)
- Liver function tests (LFT)
- Electrolytes
- Calcium (Ca)
- Phosphate (PO4)
- Thyrotrophin-stimulating hormone (TSH),
- Lactate dehydrogenase (LDH),
- Fasting glucose,
- Hemoglobin A1c (Hgb A1c),
- Amylase,
- Lipase
- Lipid panel

7.3 On Days 1 and 43 of every cycle of treatment the following assessments will be completed prior to study drug administration:

- Physical Exam
- Administration of Quality of Life Questionnaire
- Adverse Event and Concomitant medication review
- Laboratory tests including:
  - Pregnancy test when indicated (urine or serum),
  - Complete blood count with differential (CBC w/diff)
  - Comprehensive metabolic panel (CMP)
  - Liver function tests (LFT)
  - Electrolytes
  - Calcium (Ca)
  - Phosphate (PO4) (Phosphorus at UVM)
  - Thyrotrophin-stimulating hormone (TSH),
  - Lactate dehydrogenase (LDH),
  - Fasting glucose,
  - Hemoglobin A1c (Hgb A1c),
  - Amylase,
  - Lipase
  - Fasting Lipid panel

For Cycle 1 Day 1, if screening procedures were completed ≤ 7 days prior to dosing of Sunitinib, the procedures noted above in Section 7.3 do not need to be repeated.

On Days 50, 57, and 64 of every cycle of treatment, the following assessments will be completed prior to study drug administration:

- Complete blood count with differential (CBC w/diff)

Additional laboratory and imaging parameters may be assessed at any time if clinically indicated by the treating physician to ensure the safety and well-being of study participants.

During the treatment with Sunitinib, the participants will not be asked to complete diaries, however, any changes to patient dose levels or drug administration will be documented by the treating physician in the participant's medical record.

There will be a +/- 3 day window for Day 1, Day 43, Days 50, 57, and 64 of every cycle, and, a +/- 7 day window for all tumor assessment scans.**8.0 Treatment Schema:**
A cycle will be considered: Sunitinib 50mg by mouth daily for 4 weeks followed by a two week rest and Temsirolimus 25mg IV weekly for 4 weeks followed by a two week rest.

	Screening	Day 1[1]	D2-28	D29-42 Two Week Rest	D43	D50	D57	D64	D71-84 Two Week Rest
Physical Exam	X	X			X				
Sunitinib		X	X						
Medical History	X								
Temsirolimus					X	X	X	X	
Laboratory Assessments									
Complete blood count with differential (CBC)	X	X			X	X	X	X	
Comprehensive metabolic panel (CMP)	X	X			X				
Liver function tests (LFT)	X	X			X				
Electrolytes	X	X			X				
Calcium	X	X			X				
Phosphate	X	X			X				
Thyroid (TSH)	X	X			X				
LDH	X	X			X				
Fasting Glucose	X	X			X				
Hemoglobin A1c	X	X			X				
Amylase	X	X			X				
Lipase	X	X			X				
Lipid Panel	X	X			X				
Tumor Evaluation[2]	X	X							X
Pregnancy Test[4]	X	X			X				
12 Lead EKG	X								
CT Chest/Ab/Pelvis[2]	X	X							

MRI Brain [2]	X								
Quality of Life	X	X			X				

1. For Cycle 1 Day 1, if screening procedures were completed ≤ 7 days prior to dosing of Sunitinib, the procedures not need to be repeated.
2. Tumor Scans may be completed on Day 1 of each cycle and participants may begin dosing while disease assessment is being conducted as long as the patient is tolerating therapy. If disease assessment demonstrates progression of disease by RECIST 1.1 criteria, but in the opinion of the treating physician and the PI, the patient is felt to be benefiting from therapy, the patient may continue on therapy. Brain scans are only required at Screening, and will be performed only if clinically indicated throughout study.
3. End of Study visit will take place within 15 days (+/- 7 days) from the last dose of either study medication.
4. Urine or serum pregnancy testing for women of child bearing potential

8.1: Registration:

Patient registration will be done through Eryn Bagley at NCCC:

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Registration will include review of eligibility with source documentation. Eligibility will be assessed by a research nurse and the PI of the respective institutions with Ms. Bagley or her designee at NCCC. PI signature on eligibility form will be delivered via Fax or mail to Ms. Bagley.
Each patient will be assigned a unique registration number and entered into the Velos Data Base in accordance with standard operating procedure.

Treatment calendars will be generated at NCCC and be made available to treating teams at the respective institutions. CRF will be completed on site and be sent to Ms. Bagley.

9.0. Treatment Evaluation

Tumor response will be assessed by the NCI's Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines. Tumor evaluation will be performed every 12 weeks (± 7 days) while on therapy. The start of the next cycle will commence the day immediately after the completion of the prior cycle and may begin while disease assessment is being conducted as long as the patient is tolerating therapy. If disease assessment demonstrates progression of disease by RECIST 1.1 criteria, but in the opinion of the treating physician and the PI, the patient is felt to be benefiting from therapy, the patient may continue on therapy.

Tumor evaluation will include CT of Chest/Abdomen/Pelvis. Evaluation for brain and bone metastases will be performed when clinically indicated. Response criteria are provided in section 11.0.

10.0 Agents

10.1 Sunitinib: Sunitinib is an oral tyrosine kinase inhibitor which inhibits at least eight receptor protein-tyrosine kinases including vascular endothelial growth factor receptors 1–3 (VEGFR1–VEGFR3), platelet-derived growth factor receptors (PDGFRa and PDGFRb), stem cell factor receptor (Kit), Flt-3, and colony-stimulating factor-1 receptor (CSF-1R).

The recommended oral dose is 50 mg per day for 28 consecutive days with a two week (14 day) wash out. Sunitinib malate (Sutent) is commercially available and supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5mg, 25mg or 50mg of sunitinib.

Metabolism and Pharmacokinetics:
Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4. Both sunitinib and its primary metabolite bind to human plasma protein in vitro (95% and 90%, respectively). The maximum plasma concentrations (Cmax) of sunitinib are generally observed between 6 and 12 hours (Tmax) following oral administration. Food has no effect on the bioavailability of sunitinib. Sunitinib may be taken with or without food. Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours, respectively.

Toxicity:
More common side effects include: Bleeding gums; Bloating or swelling of the face, arms, hands, fingers, lower legs, or feet; Blurred vision; Chest pain; Chills; Confusion; Coughing up blood; Cracked lips; Decreased urination; Decreased urine output; Diarrhea; Difficulty in breathing or swallowing; Dilated neck veins; Dizziness; Dry mouth; Extreme fatigue; Fainting; Fast, slow, or irregular heartbeat; Fever; Headache; Increase in heart rate; Increased menstrual flow or vaginal bleeding; Irregular breathing; Labored breathing; Lightheadedness; Nervousness; Nosebleeds; Paralysis; Pounding in the ears; Prolonged bleeding from cuts; Rapid breathing; Rapid weight gain; Red or black, tarry stools; Red or dark brown urine; Shortness of breath; Sores, ulcers, or white spots on the lips, tongue, or inside the mouth; Sunken eyes; Swelling or inflammation of the mouth; Thirst Tightness in the chest; Tingling of the hands or feet; Troubled breathing; Unusual tiredness or weakness; Unusual weight gain or loss; Wheezing; Wrinkled skin; Yellow eyes or skin.

Less common side effects include: Constipation; Depressed mood; Dry skin and hair; Feeling cold Hair loss; Indigestion; Hoarseness or husky voice; Loss of appetite; Muscle cramps and stiffness Nausea; Pain in the chest, groin, or legs, especially the calves; Pain in the stomach, side, or abdomen, possibly radiating to the back; Severe, sudden headache; Slurred speech; Sudden loss of coordination; Sudden, severe weakness or numbness in the arm or leg; Sudden, unexplained shortness of breath; Vision changes; Vomiting.

Rare side effect include: Back pain; Chest discomfort; Cloudy or bloody urine; Convulsions; Darkening of the skin; Drowsiness; General feeling of tiredness or weakness; Irregular or slow heart rate; Light-colored stools; Mental depression; Skin rash; Stomach pain, continuing; Swelling of the face, feet, or lower legs.

10.2 Temsirolimus: Temsirolimus is an inhibitor of the mammailian target of rapamycin (mTOR). Its action is mediated through its binding to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR that controls cell division. In in-vitro studies using renal cell

carcinoma cell lines, temsirolimus is able to reduce levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.

Metabolism and Pharmacokinetics:
Temsirolimus is primarily metabolized through cytochrome P450 (CYP) 3A4/5. It exhibits a bi-exponential decline in whole blood concentrations and the mean half-lives of temsirolimus and sirolimus were 17.3 hr. and 54.6 hr., respectively.

Toxicity:
Common/occasional side effect include: Bladder pain; Bloody nose; Bloody or cloudy urine; Body aches or pain; Chest pain; Congestion; Cough or hoarseness; Cracked lips; Diarrhea; Difficult or labored breathing; Difficult, burning, or painful urination; Difficulty in swallowing; Dryness or soreness of throat; Fever or chills; Frequent urge to urinate; Headache; Lack or loss of strength; Lower back or side pain; Runny nose; Shortness of breath; Sneezing; Sores, ulcers, or white spots on the lips, tongue, or inside the mouth; Stomach pain; Stuffy nose; Swelling of the hands, ankles, feet, or lower legs; Swelling or puffiness of face; Tender, swollen glands in neck; Tightness in chest; Voice changes; Vomiting; Wheezing; Back pain; Blemishes on the skin; Change in taste; Difficulty having a bowel movement (stool); Difficulty with moving; Discoloration of fingernails or toenails; Dry skin; Itching skin; Loss of appetite; Loss of taste; Muscle aching or cramping; Muscle pain or stiffness; Nausea; Pain in joints; Pimples; Rash; Sleeplessness; Swollen joints; Trouble sleeping; Unable to sleep; Weight loss.

The less common side effects include: Discouragement; Feeling sad or empty; Irritability; Loss of interest or pleasure; Tiredness; Pulmonary fibrosis; Trouble concentrating.

Emergency help should be immediately employed if any of the following symptoms of suspected overdose occur: Abdominal or stomach cramps or pain; Black, tarry stools; Convulsions; Feeling that others are watching you or controlling your behavior; Feeling that others can hear your thoughts; Feeling, seeing, or hearing things that are not there; Loss of bladder control; Muscle spasm or jerking of all extremities
Severe mood or mental changes; Severe vomiting, sometimes with blood; Sudden loss of consciousness; Tenderness, pain, swelling, warmth, skin discoloration, and prominent superficial veins over affected area; Unusual behavior.

10.3 Drug Interactions:
Strong CYP3A4 inhibitors such as ketoconazole may **increase** sunitinib or temsirolimus plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme inhibition potential is recommended. Concurrent administration of these agents with the strong CYP3A4 inhibitor, ketoconazole, can result in increased drug levels. Co-administration of these agents with strong inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase drug concentrations. Grapefruit may also increase plasma concentrations of these agents.

A dose reduction for sunitinib should be considered when it must be co-administered with strong CYP3A4 inhibitors. Refer to the package insert for guidelines.

CYP3A4 inducers such as rifampin may **decrease** sunitinib and temsirolimus plasma concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. Concurrent administration of these agents with the strong CYP3A4 induce may reduce blood concentrations. Co-administration of these agents with CYP3A4 family (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John's Wort) may decrease their concentrations. St. John's Wort may decrease sunitinib plasma concentrations unpredictably. A dose increase may be considered when it must be co-administered with CYP3A4 inducers. See package insert.

Temsirolimus is also an immune suppressor and care should be taken if patients require other immunosuppressive medication during therapy such as steroids.

11.0 **Evaluation and Management of Toxicity**

Patients will be seen every six weeks at the beginning of each cycle to assess toxicity and dose. Temsirolimus is standard of therapy used throughout the United States and the world. During temsirolimus therapy, patients may be treated off site at their local oncologist's office with the approval of the PI and following notification and approval by Dartmouth's local Institutional Review Board (IRB), the Committee for the Protection of Human Subjects (CPHS). All toxicity will be managed by Dartmouth's protocol physicians and nurses for those being treated through DHMC. For those patients treated through the UVM program, the UVM research staff will manage all toxicities and report them according to the protocol. We will describe the toxicity profile of the investigational regimen by tabulating the observed toxicity according to type and grade. We will compute the rates of serious grade 3 or worse toxicity (as defined using the NCI Common Toxicity Criteria Version 4.0). Toxicity will be carefully monitored during the course of the study, but there will be no formal stopping rules. At the investigator discretion, safety labs may be drawn as standard care to assess for toxicity outside of general visit timelines. However, if the rate of grade 3 or worse non-hematological toxicity exceeds 33% at any time, accrual will be suspended and the toxicity information will be reviewed by the investigators and the Norris Cotton Cancer Center's (NCCC) Safety and Data Monitoring Committee.

11.1 Dose Modification and Monitoring of Toxicity

We will compute the rates of any toxicity and any grade 3 or worse toxicity (as defined using the NCI Common Toxicity Criteria Version 4.0). Toxicity will be carefully monitored during the course of the study, but there will be no formal stopping rules based on toxicity, as the alternating sequence of therapy use the FDA approved doses for each therapy. Temsirolimus at the FDA approved dose has already been noted to be safe following sunitinib failure. However, if the rate of grade 3 or worse non-hematological toxicity exceeds 33% at any time, accrual will be suspended and the toxicity information will be reviewed by the investigators and the NCCC's Safety and Data Monitoring Committee.

Sunitinib: (adopted from Kollmannsberger C et al., Sunitinib therapy for metastatic renal cell carcinoma: recommendations for management of side effects. Can Urol Assoc J. 2007 June: 1 (2Suppl): S41-54):

Dose modifications:
We will use the standard dose modification in 12.5 mg increments:

•Dose level 1: 50.0 mg for 4 weeks, 2 weeks off
•Dose level 2: 37.5 mg for 4 weeks, 2 weeks off
•Dose level 3: 25.0 mg for 4 weeks, 2 weeks off

Recovery to acceptable levels of toxicity should occur within 4 weeks before sunitinib or temsirolimus therapy can be continued.

Re-escalation to the previous dose level is suggested in the absence of grade 3 or higher hematologic treatment-related toxicity, or in the absence of grade 2 or higher non-hematologic treatment-related toxicity in the previous cycle.

Overall, clinical judgment based on the medical history and clinical status of individual patients should dictate the appropriate monitoring and actions, if any, to be taken in response to side effects.

Gastrointestinal Toxicity:
For grade 3 or 4 diarrhea treatment should be interrupted until diarrhea is grade 1 or less, or has returned to baseline. The sunitinib dose should be reduced by 1 dose level (12.5mg) in subsequent cycles.

Common antiemetics can be used to relieve nausea and vomiting. However, particular care should be used when sunitinib is combined with antidopaminergic agents such as domperidone, or 5HT3 antagonists, such as granisetron, ondansetron, and dolasetron, because they have been associated with QT/QTc interval prolongation or torsade de pointes.

Metabolic
Hypothyroidism has been reported in patients receiving sunitinib as early as 1–2 weeks after the initiation of therapy. No dose reduction is necessary.

For grade I or II amylase/lipase, sunitinib can continue. For grade III or IV amylase/lipase sunitinib will be discontinued and when levels return to grade I or better, may be re-initiated at the next lowest dose tier.

Hematologic
Sunitinib induces neutropenia and thrombocytopenia in about 20% of patients. For grade 3 or 4 neutropenia or thrombocytopenia, or if thrombocytopenia persists for at least 5 days, the dose of sunitinib should be reduced in the next scheduled cycle.

Erythropoietic agents such as epoetin-α or darbepoetin-α, or blood transfusions may be used at the discretion of the treating physician to treat anemia.

Hypertension
Hypertension seems to be a class effect of angiogenesis inhibitors. Patients receiving sunitinib should be monitored for hypertension and treated, as appropriate, with standard antihypertensive therapy, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium-channel

blockers (CCBs), β-blockers, and diuretics. Nondihydropyridine CCBs, such as diltiazem and verapamil, should be avoided if possible as they are known CYP3A4 inhibitors.

Sunitinib will be temporarily discontinued in patients who develop severe sustained hypertension (> 180 mm Hg systolic or > 110 mm Hg diastolic on 4 sequential BP measurements over 48 houts) or at the desecration of the treating physician. Treatment may be resumed once hypertension is controlled. If BP cannot be well controlled, patients will discontinue therapy.

Hemorrhage
For treatment-related hemorrhage, temporary discontinuation of sunitinib for mild-to-moderate epistaxis may not be necessary and may be considered only if conventional measures (e.g., tamponade) have failed. For any grade 4 hemorrhage, Sunitinib will be discontinued.

Cardiac
Left ventricular dysfunction is the main cardiac side effect of sunitinib. Patients will be monitored for congestive heart failure (CHF) and repeat EF should be done if clinically necessary. For patients with LVEF less than 50% or more than 20% below baseline, the dose of sunitinib will be interrupted and in the absence of clinical CHF, a dose reduction or discontinuation is at the discretion of the treating physician. For any clinical evidence of CHF, sunitinib will be discontinued.

Constitutional
Fatigue represents one of the most frequently encountered sunitinib-related side effects. For ≥ grade 4 fatigue, sunitinib will be discontinued and dose reduce to the next lowest dose tier once it resolves to ≤ 1. For grades ≤ grade 3, dose modification is at the discretion of the treating provider.

Skin
Hand-foot syndrome presents as painful symmetric erythematous and edematous areas on the palms and soles, commonly preceded or accompanied by paresthesias, tingling or numbness. For ≥ grade 3, sunitinib should be discontinued and after resolution to ≤ grade 1, dose reduce to the next lowest dose tier.

Temsirolimus
In general dose adjustments should be based on safety assessments, including laboratory and clinical assessments:

Dose modifications:
We will use the standard dose modification in 5 mg:
•Dose level 1: 25mg weekly for 4 weeks, 2 weeks off
•Dose level 2: 20mg weekly for 4 weeks, 2 weeks off
•Dose level 3: 15mg weekly for 4 weeks, 2 weeks off

Hematologic
Temsirolimus will be held for an absolute neutrophil count <1000 cells/mm^3, **or** platelet count <75,000 cells/mm^3, **or** any AEs ≥ grade 3 in severity. Temsirolimus can be restarted at dose reduced by 5 mg/week once AEs have resolved or lessened to ≤ grade 2.

Dose can be reduced again if necessary, but lowest dose allowed will be 15 mg/week

Gastrointestinal Toxicity:
AEs ≥ grade 3 in severity. Temsirolimus can be restarted at dose reduced by 5 mg/week once AEs have resolved or lessened to ≤ grade 2.

Metabolic
AEs ≥ grade 3 in severity. Temsirolimus can be restarted at dose reduced by 5 mg/week once AEs have resolved or lessened to ≤ grade 2.

Hgb A1C and cholesterol will be monitored and treatment initiated as clinically warranted.

Constitutional
For ≥ grade 4 fatigue, temsirolimus will be discontinued and dose reduce to the next lowest dose tier once it resolves to ≤ 1. For grades ≤ grade 3, dose modification is at the discretion of the treating provider.

12.0 Response criteria

Response criteria will use NCI's Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.

12.1 Disease evaluation

Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm)
- 10mm caliper measurement by clinical exam (when superficial)
- 20mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.

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

- Non-measurable lesions - Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques..

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes).

All measurements will be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

12.2 Methods of Measurement:
All tumor measurements and response will be assessed using RECIST 1.1. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5-7 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis.

Baseline documentation of "Target" and "Non-Target" lesions:

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

12.3 Response Criteria
Evaluation of target lesions

Complete Response (CR):

- Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR):

- At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.

Progressive Disease (PD):

- At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

- Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Evaluation of non-target lesions

Complete Response (CR):

- Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR / Non-PD:

- Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.

Progressive Disease (PD):

- Unequivocal progression of existing non-target lesions.

When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

<u>New lesions:</u>

The appearance of new malignant lesions denotes disease progression:

• The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).

• If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

• A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Evaluation of best overall response:

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

Overall Response Table **RECIST 1.1:**

Target	Non-target	New	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

12.4 Confirmation:
The main goal of confirmation of objective response is to avoid overestimating the response rate observed. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

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

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

13.0 Quality of Life
Quality of life will be assessed by the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) to assess patients. This will provide baseline data for further studies.

14.0 Evaluability:
Reporting of results:

Clinical Results: All patients included in the study will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories:

1) complete response
2) partial response
3) stable disease
4) progressive disease
5) early death from malignant disease
6) early death from toxicity
7) early death because of other cause
8) unknown (not assessable, insufficient data).

All patients who met the eligibility criteria will be included in the main analysis of the response rate. Patients in response categories 4-8 will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

15.0 Reporting Adverse Reactions:
National Institutes of Health guidelines for reporting serious adverse drug reactions will be used. In the event of a serious and unexpected adverse drug reaction, the Committee for the Protection of Human Subjects and the NCCC's Data Safety and Monitoring Board will be notified. In addition, University of Vermont PI (Dr. Steven Ades) and the UVM IRB will be notified.

Reporting of toxicity will include:

1) the likelihood of the relationship between the toxicity and treatment
2) whether the side effect noted falls within the expected toxicity profile of the agent employed
3) the severity of the toxicity

All reportable reaction are recorded and provided in report to the appropriate branches as outlined below.

Types of Report (see table):

Telephone report: For grades 4 and 5 unexpected toxicity, a telephone or electronic mail and written report will go to the following groups: Dartmouth Medical School's Committee for the Protection of

Human Subjects (CPHS), UVM IRB, and the Norris Cotton Cancer Center's Data Monitoring and Safety Committee (DMSC). The telephone or electronic mail report will be within 24 hours from when the PI is notified of the toxicity. A written report will follow within 10 working days.

If the grade 4/5 unexpected toxicity is noted at a patient being treated at UVM, they will notify the contacts at NCCC by telephone or e-mail within 24 hours. (Contacts: Dr. Lionel Lewis at lionel.d.lewis@dartmouth.edu , 603-650-8685) or Eryn Bagley (Eryn.M.Bagley@Hitchcock.ORG, 603-650-4035)

Written report: An NCI adverse drug reaction form and copies of all available and updated study data will be provided within 10 working days to the CPHS and the DMSC. All toxicity will be reported using the NIH common toxicity form.

For grades 2 and 3 unknown toxicity, a written report will be sent within 10 working days to the DMSC and the CPHS. Grades 3 or worse known toxicity will be submitted as part of the study summary**.**

Unknown Reaction	
Grades 2-3	Grades 4 and 5
Written report to CPHS and DMSC within 10 working days	Report by phone (e-mail) to CPHS and DMSC within 24 hours. Written report to follow within 10 working days.
Known Reaction	
Grades 1-3	Grades 4 and 5
Not to be reported as ADRs. A report will be submitted as part of study summary to include only ≥ grade 3.	Written report or e-mail to CPHS and DMSC within 10 working days

16.0 Ancillary support

Patients should receive full supportive care (see below), including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Steroid use is permitted at the discretion of the treating provider if necessary due to toxicity or pre-existing condition. The reason(s) for treatment, dosage, and the dates of treatment should be recorded. Supportive care for adverse reactions may include:
Acetaminophen
Meperidine
Phenothiazines
Metachlorpropamide
Lorazepam

If supportive therapy with radiation, chemotherapy or other anticancer biological agents is clinically indicated, the patient will be removed from study.

17.0 Statistical Analysis and Study Size Justification

The median time to progression from historical studies for each single agent is 11 months (sunitinib) and 4 months (temsirolimus). We hypothesize that alternating sunitinib and

temsirolimus therapy will be well tolerated and improve the combined median time to progression of the agents alone (11 + 4 months) by two (30 months). Although newer approaches to phase II trial design have been suggested, we have chosen a single arm study using an aggressive assumption of improvement of PFS (13, 14). We anticipate accrual over three years with a two year follow up.

Using nonparametric sample size calculation with a one sided test, an alpha of 0.05 and a power of 90 we would need to treat 37 patients to be able to reject the null hypothesis. We will also collect data on QOL. Scoring algorithms have been produced by the EORTC Quality of Life Study Group. A summary of the data is creating a mean for each category and using a linear transformation (15). This will allow us to estimate the effects of treatment on QOL over time.

The study is being expanded to University of Vermont Cancer Center.

18.0 STUDY CONDUCT/ETHICAL CONSIDERATIONS

The possibility of adverse events to the subjects treated in this trial is real. The possibility of benefit is also real. In compliance with Federal Regulations, as well as proper ethical conduct, the patient is required to sign a consent form once he or she is satisfied that they understand all potential outcomes, both adverse and beneficial.

A patient is free to withdraw at any time during the study. No changes will be made to the study without approval by the IRB. All changes or observations during the trial that may increase the risk will be reported to the IRB and FDA.

The Norris Cotton Cancer Center's Safety and Data Monitoring Committee (SDMC) will monitor the study progress on a quarterly basis according to our Cancer Center's guidelines. Serious or unexpected adverse events will be reported immediately by the PI to the SDMC, Dartmouth Medical School's IRB, UVMs IRB and the FDA in accordance with NIH guidelines. These activities will ensure careful oversight of patient safety.

19.0 ADDITIONAL INVESTIGATIONAL SITES GUIDING PRINCIPLE

For the convenience of study participant's the infusions of Temsirolimus may be administered at their community facility, once that facility has been approved by Dartmouth's CPHS. For community facilities with a Federalwide Assurance (FWA) and a local IRB, the CPHS will require the attainment of approval by the local IRB prior to the initial infusion of Temsirolimus. For community facilities without a Federalwide Assurance (FWA) and a local IRB, the CPHS will require a letter from a facility official (with authority to legally bind the facility) noting the facility's acknowledgement and acceptance of the obligations associated with the conduct of research at the facility. It is the duty of the DHMC-Lebanon research staff to ensure that both the local oncologist and pharmacy staff receive the study protocol, a copy of the study participant's signed informed consent, and the NIH guidelines for AE reporting.

It will be the responsibility of the principal investigator to ensure that external local treatment oncologists are trained to the standards of the protocol. Training may take place either by telephone or by direct contact with the local treating physician. A record of training will be kept in the study regulatory binder. Local oncologists will also be asked to supply documentation that they have received human subjects

protection training. A number of options for obtaining training are available on the CPHS website at: http://dartmouth.edu/~cphs/tosubmit/education/.

Research activities to be carried out at local facilities will encompass the administration of Temsirolimus. Cycle infusion doses will be calculated by investigators and pharmacy staff at DHMC – Lebanon. The completed orders will be supplied to the study participant's local facility (including local pharmacy) for use on all subsequent days in the cycle. The evaluation of each study participant on Day One of each new cycle, data supervision and management, toxicity management, and adverse event reporting will all occur at DHMC – Lebanon.

Once external site eligibility has been verified by the CPHS, study participants may begin to receive infusions at their local facility. DHMC – Lebanon study staff will ask that weekly study participant records are faxed from the local treating facility to the DHMC – Lebanon facility. Upon receipt, these records will be assessed for accuracy, protocol compliance, and adverse event notations by the DHMC – Lebanon research staff. In turn, all applicable study participant records from DHMC – Lebanon will be faxed to the local treatment facility in a timely manner.

Treating local physicians will be asked to use their best clinical judgment when treating study participants. Any significant impediments to treatment on a clinic day should immediately be reported by the local facility to the DHMC – Lebanon research team. If any reported event would justify a dose modification, DHMC – Lebanon would re-calculate the dose according to protocol, and a new order set would be sent immediately to the local facility.

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