

CTSU E2805: ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma

FAST FACTS

ELIGIBILITY CRITERIA

Pre-Registration

1. Randomization is to occur approximately 3-10 weeks post-surgery (patients must begin protocol treatment 4-12 weeks post-surgery). All patients registered either pre-surgery or post-surgery must meet 3.1.2-3.1.14 and all 3.2 criteria. Patients who do not initiate their assigned protocol treatment within the required 12-week post-operative period will be considered ineligible for this protocol, regardless of the reason for failure to start the treatment. As a result, IT IS STRONGLY RECOMMENDED that the patient is registered at least 7-10 working days prior to the 12-week post-operative limit to insure adequate time is available for shipment and receipt of the patient's assigned treatment from PMB.
2. Pre-Surgical Criteria:
 - Patients must have primary-intact renal cell carcinoma, eligible for nephrectomy with curative intent
 - Tumors ≥ 4 cm AND/OR macroscopic fully resectable nodes AND/OR surgically resectable renal vein thrombus AND/OR surgically resectable inferior vena caval thrombus by radiologic criteria to be clinically \geq pT1bNany (resectable) M0 disease
 - Multifocal ipsilateral renal cell carcinoma is allowed provided fully resectable and does not exceed inclusion criteria
3. Patients must have no history of distant metastases.
4. No prior anti-cancer therapy for renal cell carcinoma is permitted in either the adjuvant or neoadjuvant setting. This includes metastectomy for renal cell carcinoma, or radiation therapy to the renal bed.
5. Patients must be at least 18 years of age.
6. Patients must not have other current malignancies, other than basal cell skin cancer, squamous cell skin cancer, *in situ* cervical cancer, ductal or lobular carcinoma *in situ* of the breast. Patients with other malignancies are eligible if they have been continuously disease-free for ≥ 5 years prior to the time of randomization.
7. Patients must have no serious intercurrent illness including, but not limited to, clinically significant cardiovascular disease (e.g. uncontrolled hypertension, myocardial infarction, unstable angina); New York Heart Association grade II or greater congestive heart failure; serious cardiac arrhythmia requiring Medication; grade II or greater peripheral vascular disease; or psychiatric illness/social situations that would limit compliance with study requirements.
8. Patients must not have any of the following within the 6 months prior to study drug administration:
 - Myocardial infarction
 - Severe/unstable angina
 - Coronary/peripheral artery bypass graft
 - Symptomatic congestive heart failure
 - Cerebrovascular accident
 - Transient ischemic attack
 - Pulmonary embolism
9. Patient must not have ongoing ventricular cardiac dysrhythmias of NCI CTCAE Version 3.0 grade ≥ 2 . Patients with a history of serious ventricular arrhythmia (VT or VF ≥ 3 beats in a row) are also excluded. Additionally, patients with ongoing atrial fibrillation are not eligible.
10. Patients must have QTc interval < 500 msec on baseline EKG.
11. Patient must not have hypertension that cannot be controlled by medications (\geq diastolic blood pressure 100 mm Hg despite optimal medical therapy).
12. Patient must not have pre-existing thyroid abnormality with thyroid stimulating hormone that cannot be maintained in the normal range with medication.
13. If female, patient must not be pregnant or breastfeeding. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to pre-registration to rule out pregnancy. If pre-registration occurs prior to surgery, the blood or urine study must be repeated within 2 weeks prior to randomization to rule out pregnancy.

14. Women of child-bearing potential must agree to use accepted and effective method of contraception prior to study entry and for the duration of study participation.
15. Patients with known HIV are excluded due to possibility of unknown side effects on the immune system by these agents. The potential impact of pharmacokinetic interactions of retroviral therapy with sunitinib or sunitinib is unknown.

Randomization

Patients will be randomized to this trial following radical or partial nephrectomy. Randomization must occur 3-10 weeks post-surgery (patient must begin treatment 4-12 weeks post surgery) The following criteria must be met:

1. The date of randomization must be less than 12 weeks after the date of surgery weeks post surgery. Patients must have recovered from any surgical related complications.
2. Within 4 weeks prior to randomization, patients must meet preoperative eligibility requirements.
3. Patients must have histologically or cytologically confirmed renal cell carcinoma. Using 2002 (AJCC 6th edition) TNM Staging, patients must be one of the following:
 - pT1b G3-4 N0 (or pNX where clinically N0) M0
 - pT2 G(any) N0 (or pNX where clinically N0) M0
 - pT3 G(any) N0 (or pNX where clinically N0) M0
 - pT4 G(any) N0 (or pNX where clinically N0) M0 or
 - T(any) G(any) N+(fully resected) M0

Patients with microvascular invasion of the renal vein of any grade or stage (as long as M0) are also eligible. Patients must have undergone a full surgical resection (radical nephrectomy or partial nephrectomy) by either open or laparoscopic technique. Clinical evidence of lymph node positivity requires removal of all clinically positive nodes. Surgeons should designate extent of node dissection in Appendix V. All surgical specimens must have negative margins. Patients with positive renal vein margins are eligible unless there is invasion of the renal vein wall at the margin (provided no other margins are positive).
4. Patients must not have collecting duct carcinomas or medullary carcinomas.
5. Patients must have an ECOG performance status of 0-1.
6. Patients must have an absolute baseline left ventricular ejection fraction of $\geq 50\%$ by MUGA scan within 4 weeks prior to registration.
7. Patients must have paraffin-embedded tumor specimen available for central core review of tumor histology and other correlative studies.
8. Patients must have no evidence of residual or metastatic renal cell cancer as documented on CT scans of the chest, abdomen, and pelvis, all with oral and IV contrast (MRI scans of the abdomen and pelvis with gadolinium and a non-contrast CT of the chest may be substituted if patient is not able to have CT scans with intravenous contrast). Patients unable to tolerate either gadolinium or IV contrast should not participate in this study (limitations to a patient's renal function should be taken into consideration when screening for this study). Scans must be obtained within 4 weeks of randomization. Changes on these scans that are felt to be post surgical must be documented. Patients without reported lymph nodes in the resected surgical specimen and a reported pathologic stage (post-nephrectomy) of pNX MUST undergo a postoperative contrast-enhanced CT scan (or MRI with gadolinium) within 4 weeks of randomization to document that there is no evidence of residual disease.
9. Patients must not be taking cytochrome P450 enzyme-inducing antiepileptic drugs (phenytoin, carbamazepine or Phenobarbital), St. John's Wort, ketoconazole, dexamethasone, the dysrhythmic drugs (i.e. terfenadine, quinidine, procainamide, sotalol, probucol, bepridil, indapamide or flecainide), haloperidol, risperidone, rifampin, grapefruit or grapefruit juice within two weeks of randomization and during the course of therapy (see Appendix XII has a list of additional medications which have the potential for interaction. Medications are not prohibited unless listed above). Topical and inhaled steroids are permitted.
10. Patients must not receive any other investigational anti-cancer agents during the period on study.
11. Patients must not have a serious intercurrent illness including, ongoing or active infection requiring parental antibiotics.
12. Patients must be able to swallow pills.
13. Patients must have the following laboratory values within 4 weeks of randomization:
 - AGC $\geq 1,500/\text{mm}^3$
 - Platelet Count $\geq 100,000/\text{mm}^3$

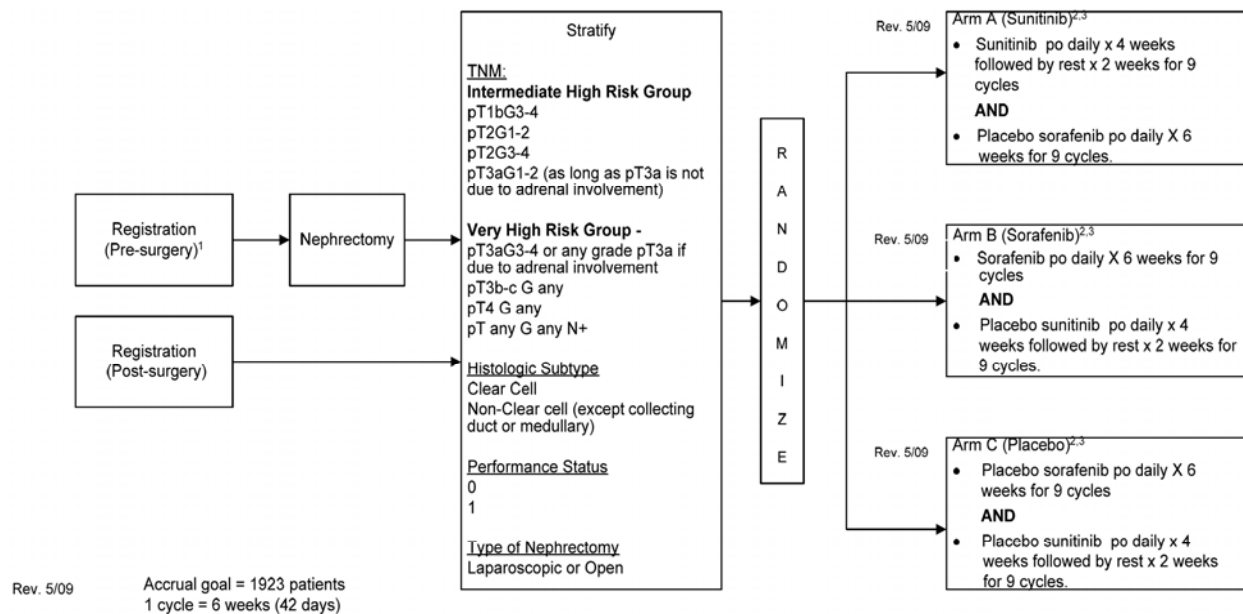
- Serum Creatinine $\leq 2.0 \times \text{ULN}$ or Calculated Creatinine Clearance $\geq 30 \text{ ml/min}$
- Total Bilirubin $\leq 1.5 \times \text{ULN}$
- SGOT and SGPT $\leq 2.5 \times \text{ULN}$

PRE-STUDY PARAMETERS

1. H&P/Blood Pressure/Vital Signs/ECOG Performance Status
2. CBC (with differential and platelet count), Chemistries (Na, K, Cl, CO₂, BUN, creatinine), LDH, hemoglobin, Liver function tests (SGOT, SGPT, total bilirubin), serum calcium, albumin, total protein, and alkaline phosphatase. **TSH, T4, T3U at baseline, cycle 1, cycle 2 and as needed thereafter.** Patients not on anticoagulation therapy must have PT, PTT, and INR measured at baseline only. Patients taking warfarin for therapeutic anticoagulation must have their INR measured weekly for the first cycle, then once per cycle thereafter; these patients must also have PT and PTT measured every cycle. Follow-up labs can be obtained +/- 5 days.
3. CT Scan of chest, abdomen, and pelvis with IV and oral contrast. MRI scan of the abdomen and pelvis with gadolinium and a non-contrast CT of the chest may be substituted if patient is not able to have CT scans with intravenous contrast. If gadolinium is contraindicated, please contact the study chair, Dr. Naomi Haas, for further instructions.
4. EKG
5. MUGA Scan
6. Beta HCG for women with child bearing potential
7. Urine for DNA methylation studies – Urine 30 cc should be collected within 3 weeks prior to or at the time of nephrectomy, 2 weeks prior to therapy, month 3 and 6 and at definite recurrence.
8. Biological Samples – See Section 7.2 for sample submission requirements at baseline and recurrence.

Note: See section 7.1 for complete details for pre-study requirements

TREATMENT PLAN



1. All patients must be registered either pre- or post-surgery. Physicians are strongly urged to register patients prior to radical or partial nephrectomy so that fresh tissue can be procured for correlative endpoints at the time of surgery; however, patients may participate in this Phase III trial even if they are registered following surgery.

Rev. 7/09 2. Biopsy at recurrence.

Rev. 5/09 3. Patients should start sunitinib / placebo at 37.5mg (3 x 12.5mg) orally once daily and sorafenib / placebo at 400mg (2 x 200mg) orally once daily with subsequent **mandatory escalation** to sunitinib / placebo at **50mg** (4 x 12.5mg) orally once daily and sorafenib / placebo at 400mg (2 x 200mg) orally **twice** daily at the beginning of cycle 2 or 3 if **ONLY** grade 1 or lower toxicity has occurred in the preceding cycle. In addition, dose escalation at the beginning of cycle 2 or 3 is allowed if the most severe grade of toxicity in the preceding cycle is grade 2.

Rev. 4/07, 9/08 NOTE: Patients with cT1b-T4N0 or any fully resectable (N1-2)M0 disease should be included in pre-operative registration.

Rev. 9/08 NOTE: Please see Section 3.2.3 for post-operative staging requirements.