Everolimus/placebo provided

1. Patients must have histologically or cytologically confirmed renal cell carcinoma (clear cell or non-clear cell allowed, but collecting duct or medullary carcinomas excluded). Patients must be considered pathologically either Intermediate High Risk or Very High Risk as defined in Section 4.0. Patients must not have a history of distant metastases. Patients with microvascular invasion of the renal vein of any grade or stage (as long as M0) are also eligible.

2. Patients must have undergone a full surgical resection (radical nephrectomy or partial nephrectomy), including removal of all clinically positive nodes. Surgical margins must be negative. 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). Patients must plan to start study drug within 84 days after the date of full surgical resection. Patients must have recovered from any surgical related complications.

3. Patients with bilateral renal tumors are eligible provided both tumors have undergone full surgical resection and at least one of the tumors meets all eligibility criteria above (#1 and #2). Patients must plan to start study drug within 84 days after the date of the resection of the first tumor.

4. Patients must not have any evidence of residual or metastatic renal cell cancer on CT scan of the chest, abdomen, and pelvis, all with oral and IV contrast after nephrectomy and within a maximum of 28 days prior to registration. An MRI scan of the abdomen/pelvis with gadolinium and a non-contrast CT of the chest is an acceptable imaging alternative. Non-contrast CT of the chest/abdomen/pelvis should only be performed if, in the opinion of the investigator, it is in the best medical interest of the patient to not receive IV contrast of any form. NOTE: PET/CT is not an acceptable imagining alternative. Patients who display subcentimeter pulmonary nodules (by CT scan) that are non-specific and considered unlikely to represent metastatic disease by the treating investigator will be considered eligible.

5. Patients must be offered the opportunity to participate in specimen banking for future use to include the translational medicine studies outlined in Section 15.0.

6. Patients must not have received any prior anti-cancer therapy (except for radical or partial nephrectomy noted above) for renal cell carcinoma, including systemic therapy in the adjuvant or neoadjuvant setting, immunotherapy, investigational therapy, surgical metastastectomy, or radiation therapy.

7. Patients must not be planning to receive other anti-cancer agents including investigational agents while on protocol treatment.

8. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed.

9. Patients must not have received immunization with an attenuated live vaccine within seven days prior to registration nor have plans to receive such vaccination while on protocol treatment.

10. Patients must have a complete physical examination and medical history within 28 days prior to registration.

11. Patients must not be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors, (e.g. ketoconazole, itraconazole, voriconazole, posaconazole, fluvoxamine, nefazodone, nelfinavir, ritonavir) and/or strong CYP3A4 inducers (e.g. phenytoin, rifampin, rifabutin) within 14 days prior to randomization. (Moderate inhibitors or inducers of isoenzyme CYP3A4 should be avoided, but if necessary can be used with caution. See Section 7.1c.)

12. Patients must not have any Grade III/IV cardiac disease as defined by the New York Heart Association Criteria (i.e., patients with cardiac disease resulting in marked limitation of physical activity or resulting in inability to carry on any physical activity without discomfort), unstable angina pectoris, myocardial infarction within 6 months, or serious uncontrolled cardiac arrhythmia. See Appendix 19.1.

13. Patients must not have any known uncontrolled underlying pulmonary disease (e.g. FEV1 or DLCO 50% or less of predicted OR O2 saturation 88% or less at rest on room air).

14. Patients must not have any known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients.

15. Patients must have absolute neutrophil count (ANC) ≥ 1,500/mcL, platelet count ≥ 100,000/mcL and hemoglobin ≥ 9.0 g/dl obtained within 28 days prior to registration.
16. Patients must have serum creatinine ≤ 2.0 x upper limit of normal (ULN) or calculated creatinine clearance (CrCl) ≥ 30mL/min obtained within 28 days prior to registration.

17. Patients must have bilirubin ≤ 1.5 x ULN, and SGOT and SGPT ≤ 2.5 x ULN obtained within 28 days prior to registration.

18. Patients must NOT have liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh Class C). NOTE: A detailed assessment of Hepatitis B/C medical history and risk factors must be done at screening for all patients. HBV and HCV testing are required at screening for all patients with a positive medical history based on risk factors and/or confirmation of prior HBV/HCV infection. (See Section 9.0 for testing information and Section 8.6 for management of patients with positive testing.)

19. Patients must not have a known history of HIV seropositivity.

20. Patients must not have uncontrolled hyperlipidemia (fasting serum cholesterol >300 mg/dL AND fasting triglycerides > 2.5xULN) obtained within 28 days prior to registration. Optimal lipid control must be achieved before registration and monitored during protocol treatment (see Section 8.4b).

21. Patients must not have uncontrolled diabetes mellitus (defined by fasting serum glucose >1.5xULN) obtained within 28 days prior to registration. Optimal glucose control must be achieved before registration and monitored during protocol treatment (see Section 8.4b).

22. Patients must be able to take oral medications. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of everolimus (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).

23. Patients must have a Zubrod Performance Status of 0 or 1 (see Section 10.3).

24. All patients must be 18 years of age or older.

25. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

26. Patients must be pregnant or nursing due to animal studies that have shown reproductive toxicity effects. Women/men of reproductive potential must have agreed to use an effective contraceptive method during protocol treatment and up to 8 weeks after ending protocol treatment. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

27. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

28. As part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

Pre-study Parameters
1. History and physical including weight and performance status; Hepatitis B/C screening (those at high risk should undergo lab testing, see section 7.1d)
2. Labs including CBC with differential; bilirubin, AST, ALT, Alk Phos, serum creatinine, fasting glucose, cholesterol, and triglycerides
3. Scans including CT chest/abdomen/pelvis; bone scan recommended if rising alk phos or bone pain

Treatment

<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSE</th>
<th>ROUTE</th>
<th>DAYS</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus or</td>
<td>10 mg (two 5 mg</td>
<td>Oral</td>
<td>Every Day</td>
<td>378 days (54 weeks)</td>
</tr>
<tr>
<td>Matched Placebo</td>
<td>Tablets)</td>
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