

TYPE OF CANCER: Metastatic Clear Cell Carcinoma of the
Kidney
TYPE OF TRIAL: Phase II
TRIAL SPONSOR: Novartis

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STUDY SUMMARY

A randomized, open label, multi-center phase II study to compare bevacizumab plus RAD001 versus interferon alfa-2a plus bevacizumab for the first-line treatment of patients with metastatic clear cell carcinoma of the kidney

TREATMENT OVERVIEW

- Patients will be randomized to receive either bevacizumab intravenously every 2 weeks plus RAD001 orally daily or interferon alfa-2a subcutaneously 3 times weekly plus bevacizumab intravenously every 2 weeks

PRE-TREATMENT ASSESSMENTS

- Informed consent
- Medical history
- Vital signs
- Physical exam
- Skin biopsy (if applicable)
- Performance status
- Hematology
- Serum Chemistry
- Coagulation studies
- Lipid profile
- Urinalysis
- Pregnancy test (if applicable)
- CT or MRI with contrast of the Chest, Abdomen , and Pelvis
- Brain MRI or CT
- Bone scan
- ECG
- Other study specific labs

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

Inclusion criteria

1. Age \geq 18 years old

2. Patients with metastatic renal cell carcinoma and with histological or cytological confirmation of clear cell RCC (pathology report based on the tissue from the original diagnosis of renal cell cancer is acceptable). Any percentage of clear cell histology is acceptable.
3. Patients with at least one measurable lesion at baseline as per the RECIST criteria. If skin lesions are reported as target lesions, they must be documented (at baseline and at every physical exam) using color photography and a measuring device (such as a caliper) in clear focus to allow the size of the lesion(s) to be determined from the photograph.
4. Patients with progressive metastatic renal cell carcinoma (by RECIST criteria) requiring treatment.
5. Patients who had a prior partial or complete nephrectomy. Partial nephrectomy is allowed only if the resection margins were clearly negative.
6. Patients with a Karnofsky Performance Status $\geq 70\%$.
7. Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9/L$, Platelets $\geq 100 \times 10^9/L$, Hb >9 g/dL.
8. Adequate liver function: serum bilirubin: $\leq 1.5 \times$ ULN, ALT and AST $\leq 2.5 \times$ ULN. Patients with known liver metastases: AST and ALT $\leq 5 \times$ ULN.
9. Adequate renal function: serum creatinine $\leq 2.0 \times$ ULN.
10. INR and PTT ≤ 1.5 . (Anticoagulation is allowed if target INR ≤ 1.5 on a stable dose of warfarin or on a stable dose of LMW heparin for >2 weeks at time of randomization.)
11. Adequate lipid profile: total cholesterol < 300 mg/dL and triglyceride < 200 mg/dL.
12. Women of childbearing potential must have had a negative serum pregnancy test 72 hours prior to the administration of the study treatment start.
13. Patients who give a written informed consent obtained according to local guidelines.

Exclusion criteria

1. Patients within 4 weeks post-major surgery (e.g., intra-thoracic, intra-abdominal or intrapelvic), open biopsy, or significant traumatic injury to avoid wound healing complications. Minor procedures and percutaneous biopsies or placement of vascular access device require 7 days prior to study entry.
2. Patients who had radiation therapy within 28 days prior to start of study treatment (palliative radiotherapy to bone lesions allowed within 2 weeks prior to study treatment start).
3. Patients in anticipation of the need for major surgical procedure during the course of the study.
4. Patients with a serious non-healing wound, ulcer, or bone fracture.
5. Patients with a history of seizure(s) not controlled with standard medical therapy.

6. Patients who have received prior systemic treatment for their metastatic RCC. Adjuvant immunotherapy (vaccines acceptable, but no cytokines) completed 3 months prior to study treatment start is acceptable.
7. Patients who received prior therapy with VEGF pathway inhibitor (even in the adjuvant setting), such as sunitinib, sorafenib, and bevacizumab.
8. Patients who have previously received systemic mTOR inhibitors (sirolimus, temsirolimus, everolimus).
9. Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients.
10. Patients with evidence of current central nervous system (CNS) metastases or spinal cord compression.
11. Patients with a history of abdominal fistula, gastrointestinal perforation, or intraabdominal abscess within 6 months prior to study enrollment.
12. Patients with proteinuria at screening as demonstrated by either:
 - Urine protein: creatinine (UPC) ratio ≥ 1.0
 - Urine dipstick for proteinuria $\geq 2+$ (patients discovered to have $\geq 2+$ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate $\leq 1\text{g}$ of protein in 24 hours to be eligible).
13. Patients with inadequately controlled hypertension (defined as a blood pressure of > 150 mmHg systolic and/or > 100 mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy.
14. Patients receiving ongoing or with recent (within 10 days prior to study treatment start) need for full therapeutic dose of oral or parenteral anticoagulants or chronic daily treatment with aspirin (> 325 mg/day) or clopidogrel (>75 mg/day).
15. Patients receiving chronic systemic treatment with corticosteroids (dose of ≥ 10 mg/day methylprednisone equivalent) or another immunosuppressive agent. Inhaled and topical steroids are acceptable.
16. Patients with a known history of HIV seropositivity.
17. Patients with hypersensitivity to interferon alfa-2a or any component of the product.
18. Patients with an active, bleeding diathesis or coagulopathy or recurrent thromboembolism (>1 episode of DVT/PE during the past year).
19. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
 - unstable angina pectoris, symptomatic congestive heart failure (NYHA II, III, IV), myocardial infarction ≤ 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia, cerebrovascular accidents ≤ 6 months before study treatment start
 - severely impaired lung function as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O₂ saturation that is 88% or less at rest on room air
 - poorly controlled diabetes as defined by fasting serum glucose $>2.0 \times$ ULN

- any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study
 - nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study treatment, such as, severe hypertension that is not controlled with medical management and thyroid abnormalities whose thyroid function cannot be maintained in the normal range by medication
 - liver disease such as cirrhosis, decompensated liver disease, chronic active hepatitis or chronic persistent hepatitis.
20. Patients who have a history of another primary malignancy and off treatment for ≤ 3 years, with the exception of non-melanoma skin cancer and carcinoma in situ of the uterine cervix.
21. Female patients who are pregnant or breast feeding, or adults of reproductive potential who are not using effective birth control methods. If barrier contraceptives are being used, these must be continued throughout the trial by both sexes. Oral contraceptives are not acceptable.
22. Patients who are using other investigational agents or who had received investigational drugs ≤ 4 weeks prior to study treatment start.
23. Patients unwilling to or unable to comply with the protocol.