Supplementary Data

Table S1. Inclusion and Exclusion Criteria

Inclusion criteria	• Aged ≥18 years • Histologically confirmed RCC with a clear cell component • Documented PD • Measurable disease by RECIST criteria • ≤1 prior VEGFR-targeted therapy; no prior treatment with mTOR-targeted drugs • Karnofsky performance status >70%, life expectancy ≥3 months • Ability to give written informed consent
Exclusion criteria	• Known hypersensitivity to temsirolimus or its metabolites (including sirolimus), polysorbate 80, or any other component of the temsirolimus formulation • Primary CNS malignancies or active CNS metastases • Hematologic malignancies (ie, leukemia, lymphoma, and multiple myeloma) • Hematologic abnormalities (hemoglobin <9.0 g/dL; ANC <1500/mm^3; platelets <100,000/mm^3) • Serum chemistry abnormalities (fasting serum cholesterol >350 mg/dL; fasting triglycerides >400 mg/dL; total bilirubin >1.5 × ULN; AST or ALT >2.5 × ULN (or >5 ×

ULN in patients with liver metastasis); serum albumin <3.0 g/dL; creatinine >1.5 × ULN [or calculated creatinine clearance <50 mL/m/1.73 m^2]; proteinuria >2.5 g/24-h or 3+ with urine dipstick)

- Significant cardiovascular disease (ie, active clinically symptomatic left ventricular failure, active hypertension [diastolic blood pressure >100 mmHg; patients with a history of hypertension must have been stable on anti-hypertensive drugs for ≥4 weeks], uncontrolled hypertension [blood pressure >140/90 mmHg on ≥2 antihypertensive medications], and myocardial infarction ≤3 months prior to first dose of study drug)
- Patients with delayed healing of wounds, ulcers, and/or bone fractures
- Pulmonary hypertension or pneumonitis
- Serious/active infection; infection requiring parenteral antibiotics
- Inadequate recovery from any prior surgical procedure; major surgical procedure within 6 weeks prior to study entry
- Uncontrolled psychiatric disorder, altered mental status precluding informed consent or necessary testing
- Inability to comply with protocol requirements

- Ongoing hemoptysis or history of clinically significant bleeding
- Cerebrovascular accident ≤12 months of study entry, or peripheral vascular disease with claudication on walking <1 block
- Deep venous thrombosis or pulmonary embolus ≤6 months of study entry and/or ongoing need for full-dose oral or parenteral anticoagulation
- Patients with a "currently active" second primary malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed anticancer therapy and are considered by their physician to be <30% risk of relapse
- Pregnant or lactating women; all male and female fertile patients must use adequate contraception (barrier method) while on study and for 3 months thereafter
- Known concomitant genetic or acquired immune suppression disease, such as HIV

RCC, renal cell carcinoma; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; CNS, central nervous system; ANC, absolute neutrophil count; ULN, upper limit of normal; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table S2. DLT Criteria

Definition of the MTD

- The maximum dose at which ≤1 of 3–6 patients in a dose group experience a drug-related DLT during treatment cycle 1
- The MTD will not be established until all patients entered into the dose level under evaluation have completed cycle 1 (or have discontinued further participation in the study due to the occurrence of a DLT)

The occurrence of any of the following drug-related toxicities were considered to be DLTs

1. Grade 3 nonhematologic toxicity lasting >3 days despite optimal supportive care with the exception of
    - Alopecia
    - Grade 3 rash, if tolerated by the subject
    - Grade 3 manageable hypertension
    - Grade 3 self-limited or medically controllable toxicities (eg, fever without neutropenia, nausea, vomiting, fatigue)
    - Grade 3 AST or ALT lasting for ≥1 week
2. Grade 4 nonhematologic toxicity
3. Neutropenia that is
    - Grade 3/4 associated with fever (oral temperature >39ºC) and requiring antibiotic therapy
    - Grade 4 and sustained (duration >5 days)

4. Grade 4 thrombocytopenia (ie, platelets <25,000/mm^3)

5. Toxicity of any grade that results in interruption of treatment for >2 weeks

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DLT, dose-limiting toxicity; MTD, maximum tolerated dose; AST, aspartate aminotransferase; ALT, alanine aminotransferase.