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TREATMENT OF REFRACTORY METASTATIC RENAL CELL CARCINOMA (RCC) WITH LENVATINIB (E7080) AND EVEROLIMUS

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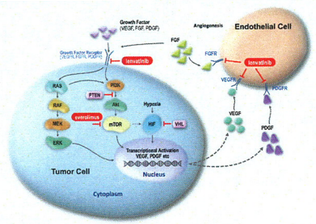
BACKGROUND

- Renal cell carcinoma (RCC) is generally resistant to chemotherapy, radiotherapy, and hormone therapy. Improved understanding of the molecular basis of RCC has meant that treatment options have evolved from being predominantly cytokine-based to being dominated by targeted agents with development and approval of targeted therapies (inhibitors of the mammalian target of rapamycin [mTOR] and vascular endothelial growth factor [VEGF] pathways) that have shown clinical benefit in patients with metastatic RCC.
- Angiogenesis has been identified as a key factor in development of the disease. A major component of the angiogenic process in RCC is VEGF. An alternative pathway is mediated by mTOR, which is downstream of phosphoinositide 3-kinase and protein kinase B. mTOR is a protein kinase that regulates cell growth, cell proliferation, cellular metabolism, and angiogenesis.
- There is no randomized study to date to indicate that combination therapy in second-line treatment of metastatic RCC provides significant advantage over single-agent therapy. It is hypothesized that, by using an mTOR inhibitor in combination with a VEGF receptor (VEGFR) inhibitor, blockade could take place at 2 levels of the pathways activated in RCC (**Figure 1**) and this may overcome an aspect of resistance that may develop through feedback mechanisms with single-agent therapy.[1]

Figure 1. Hypothesized simplified representation of signaling pathways involved in renal cell carcinoma inhibited by lenvatinib and everolimus.[1,2]



Akt, protein kinase B; ERK, extracellular signal-regulated kinase; FGF, fibroblast growth factor; FGFR, FGF receptor; HIF, hypoxia-inducible factor; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PI3K, phosphatidylinositol phosphate-3 kinase; PTEN, phosphatase and tensin homolog; RAF rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma oncogene protein; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; VHL, von-Hippel-Lindau tumor suppressor protein.

- Lenvatinib is an oral tyrosine kinase inhibitor hypothesized to target VEGFR 1-3, fibroblast growth factor receptor 1-4, RET, KIT, and platelet-derived growth factor receptor beta. Lenvatinib has demonstrated acceptable toxicity and antitumor activity in phase 1 and 2 studies.[3-5]
- Everolimus, an oral mTOR inhibitor, is approved for treatment of patients with advanced RCC whose disease has progressed on or after treatment with VEGF-targeted therapy.
- This multicenter, randomized, open-label, phase 1b/2 study investigates everolimus in combination with the investigational agent lenvatinib in RCC patients with unresectable or metastatic disease (NCT01136733). The study will be conducted in 2 phases: a phase 1b dose-escalation component to assess safety and tolerability and to determine the maximally tolerated dose (MTD) of the combination, and a 3-arm randomized phase 2 component to compare the safety and efficacy of the 2 investigational arms (Arm A combination dosing and Arm B single-agent lenvatinib) with the comparator (Arm C single-agent everolimus).

PRIMARY OBJECTIVES

- **Phase 1b:** To determine the dose-limiting toxicities (DLTs) and MTD, and establish the recommended phase 2 (RP2) dose for lenvatinib in combination with everolimus in patients with unresectable advanced or metastatic RCC.
- **Phase 2:** To compare the progression-free survival (PFS) of (1) lenvatinib in combination with everolimus at the RP2 dose once daily (Arm A) and (2) single-agent lenvatinib 24 mg once daily (Arm B) with single-agent everolimus 10 mg once daily (Arm C) in patients with unresectable advanced or metastatic RCC and disease progression following 1 prior VEGF-targeted treatment.

METHODS

Overall Study Design

- **Phase 1b:** Dose escalation will be performed to determine the MTD of the combination; starting doses are lenvatinib 12 mg/day and everolimus 5 mg/day. A cohort expansion will follow at the MTD. When all dose escalation cohort patients have completed Cycle 1 and all MTD expansion cohort patients have completed Cycle 2, all patients' DLTs, safety, and clinical data will be reviewed to confirm whether phase 2 randomization may commence and to recommend a combination dose for phase 2.
- **Phase 2:** Approximately 150 patients, previously treated with 1 VEGF-targeted treatment for unresectable advanced or metastatic RCC, will be randomized into 3 arms (**Figure 2**) to compare the safety and efficacy of these 3 regimens.

Primary Endpoint

- **PFS:** Primary comparison of PFS is between Arm A (Arm B) and Arm C.

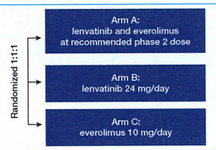
Secondary Endpoints

- Secondary comparison of PFS is between Arm A and Arm B.
- Overall survival.
- Objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), and durable stable disease rate (SD ≥23 weeks).
- To assess pharmacokinetic (PK) profiles.
- To assess PK and pharmacodynamic (PD) relationship.

Exploratory Objectives

- To explore blood and tumor biomarkers that correlate with efficacy-related endpoints of this study.
- To evaluate the role of DNA sequence variability on absorption, distribution, metabolism, excretion, and susceptibility to adverse events of lenvatinib.

Figure 2. Phase 2 study design.[a]



[a]Stratification by hemoglobin and corrected serum calcium.

Patients

- Patients ≥18 years of age with histologically confirmed diagnosis of RCC and evidence of unresectable advanced or metastatic RCC, Eastern Cooperative Oncology Group performance status of 0 or 1, and adequate organ function are eligible.
- For phase 1, patients with any number of lines of prior therapy are eligible.
- For phase 2, patients treated with 1 prior VEGF-targeted treatment for unresectable advanced or metastatic RCC are eligible.
- Key inclusion and exclusion criteria are summarized in **Table 1**.

Table 1. Key Inclusion and Exclusion Criteria

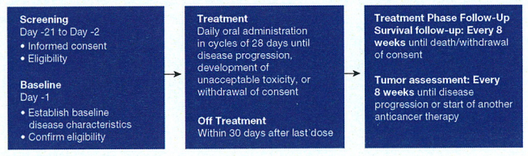
Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed diagnosis of RCC and documented evidence of unresectable advanced or metastatic RCC • ECOG performance status of 0 or 1 • Adequately controlled blood pressure (BP); BP ≤150/90 mm Hg at screening • Adequate renal, liver, and bone marrow function • INR ≤1.5 • ≥18 years of age • Negative pregnancy and effective contraception • Voluntary written informed consent	• Anticancer treatment within 21 days or any investigational agent within 30 days prior to first dose of study drug (should have recovered from any toxicity related to previous anticancer treatment) • Major surgery within 3 weeks prior to first dose of study drug • Urine protein ≥1 g/day • Uncontrolled diabetes as defined by fasting serum glucose >1.5 x ULN • Fasting total cholesterol >7.75 mmol/L (>300 mg/dL) • Fasting triglyceride level >2.5 x ULN • GI malabsorption, GI anastomosis, or any other condition that might affect absorption of study drugs • Significant cardiovascular impairment • Bleeding disorder or thrombotic disorder requiring anticoagulant therapy necessitating therapeutic INR monitoring • Active hemoptysis within 3 weeks prior to first dose of study drug
	• **Phase 1b:** Patients who discontinued prior tyrosine kinase inhibitor due to toxicity • **Phase 1b:** Patients with untreated or unstable metastases to the CNS
• **Phase 2:** Histologic or cytologic confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable) • **Phase 2:** Radiographic evidence of disease progression according to modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) on or within 6 months of stopping prior therapy • **Phase 2:** Measurable disease per RECIST 1.1	• **Phase 2:** Patients with CNS (eg, brain or leptomeningeal) metastases • **Phase 2:** Prior exposure to lenvatinib or mTOR inhibitor • **Phase 2:** Active malignancy (excluding RCC, melanoma in-situ, basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix) within past 24 months

CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; GI=gastrointestinal; INR=international normalized ratio; mTOR=mammalian target of rapamycin; RCC=renal cell carcinoma; ULN=upper limit of normal.

Treatment and Assessment Schedule (Figure 3)

- Patients will receive daily treatment in cycles of 28 days.
- Tumor assessments will be performed every 8 weeks according to RECIST 1.1 until disease progression or start of another anticancer therapy.

Figure 3. Treatment and assessment schedule.



- Dose interruptions and reductions are to follow protocol-specific instructions for management of study drug–related adverse events ≥Grade 2, with additional instructions to be followed for management of known toxicities of VEGF inhibitors and mTOR inhibitors, including hypertension, proteinuria, noninfectious pneumonitis, and elevations in blood glucose and lipids.
- Key study assessments are summarized in **Table 2**.
  - PK sampling
    - All patients (excluding phase 2 full PK profile sampling subset, see below): PK sampling predose and 2 to 8 hours postdose on Day 1 of Cycles 1, 2, and 3.
    - Phase 2 only: 9 to 12 patients in each of the 3 treatment arms will participate in the phase 2 full PK profile sampling subanalysis set. On Day 15 of Cycle 1, sampling to occur predose, 30 minutes postdose, and 1, 2, 3, 4, 8, 12, and 24 hours postdose.
  - PD sampling, phase 2 only
    - Collection of archived tumor biopsy sections unless no such material is available.
    - Mandatory collection of blood to obtain genomic DNA.
    - Mandatory collection of blood to obtain plasma, serum, or other components to be used for biomarker studies. Sampling at baseline (predose), Day 15 of Cycle 1, and predose Day 2 of all subsequent cycles and at the off-treatment assessment.

Table 2. Summary of Key Study Assessments

Screening/Baseline	Cycle X Day 1	Cycle X Day 15[a]	Off Treatment	Follow-Up
Informed consent Eligibility assessment Demographic Medical history; prior and concomitant medications				
Physical examination/ vital signs	Physical examination; vital signs	Vitals[a]	Physical examination; vital signs	
Urinalysis	Urinalysis	Urinalysis[a]	Urinalysis	
ECOG/NYHA	ECOG		ECOG	
Clinical chemistry; hematology	Clinical chemistry; hematology		Clinical chemistry; hematology	
AJCC staging				
12-lead ECG	12-lead ECG			
MUGA	MUGA every 16 weeks		MUGA	
Pregnancy test as applicable			Pregnancy test as applicable	
	AEs/SAEs Assessed Throughout			
Tumor assessments	Tumor assessments every 8 weeks or sooner if clinically indicated		Tumor assessments[b]	Tumor assessments[c] Survival[d]

AEs=adverse events; AJCC=American Joint Committee on Cancer; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; MUGA=multiple gated acquisition; NYHA=New York Heart Association; SAEs=serious AEs.
[a]Cycle 2 Day 15 scheduled visit to include vitals, urinalysis, hematology, and clinical chemistry. Subsequent to Cycle 2, patients with elevated blood pressure (systolic ≥160 mm Hg or diastolic ≥100 mm Hg) and/or proteinuria ≥Grade 2 will have additional blood pressure monitoring and urinalysis performed on Day 15 of every cycle or more frequently if clinically indicated.
[b]Only necessary if >30 days since previous assessment.
[c]Patients who have gone off study without progression should have tumor assessments every 8 weeks until disease progression is documented or another anticancer therapy is initiated.
[d]For patients who have discontinued study treatment, survival data will be collected every 8 weeks.

Statistical Considerations

- There is no statistical comparison for phase 1b.
- Phase 2 primary analysis will be performed at the end of the randomization phase (when a total of at least 90 PFS events among the 3 treatment arms and at least 60 PFS events among Arm A [or Arm B] and Arm C have been observed).
- Primary analysis of PFS will be based on investigator assessment by RECIST 1.1.
- **Analysis sets** are defined as:
  - **Safety Analysis Set** will include all patients who received at least 1 dose of study drug and had at least 1 postbaseline safety evaluation. This will be the analysis set for all safety evaluations (phase 1 and phase 2).
  - **Full Analysis Set (Intention-to-Treat Analysis Set)** will include all randomized patients. This will be the primary analysis set for efficacy, as well as for demographics and baseline characteristics (phase 2).
  - **Per-Protocol Analysis Set** will include patients who received at least 1 dose of assigned study drug, had no major protocol violations, and had both baseline and postbaseline tumor assessments. Patients for whom death occurred prior to the first postbaseline tumor assessment will also be included. The Per-Protocol Analysis Set will be the secondary analysis set for efficacy (phase 2).
- For phase 2, PFS will be analyzed using Kaplan-Meier product-limit estimates and compared between treatment groups using the stratified logrank test with hemoglobin (≤13 g/dL vs >13 g/dL for males; and ≤11.5 g/dL vs >11.5 g/dL for females) and corrected serum calcium (≥10 mg/dL vs <10 mg/dL) as stratification factors. Median PFS for each arm will be presented with 2-sided 95% confidence intervals (CIs).
- Median survival time and cumulative probability of survival at 12, 18, and 24 months will be calculated using Kaplan-Meier product-limit estimates for each treatment arm and presented with 2-sided 95% CIs.
- ORR, DCR, CBR, and durable stable disease rate will be calculated with exact 95% CIs using the method of Clopper and Pearson.

RESULTS

- Three phase 1b dose-escalation cohorts and the expansion cohort have completed enrollment. Enrollment of phase 2 commenced in March 2012 and accrual of 150 patients is ongoing. Participating phase 2 centers are located in the United States, United Kingdom, Spain, Poland, and Czech Republic and are expected to enroll patients throughout 2012.

CONCLUSIONS

- The ongoing phase 2 part of this study will evaluate safety and efficacy of 2 investigational arms (Arm A combination dosing and Arm B single-agent lenvatinib) with the comparator (Arm C single-agent everolimus) in refractory renal cell carcinoma (RCC) patients.
- To the authors' knowledge, this will potentially be the first randomized study in refractory RCC patients to report the progression-free survival of a combination therapy regimen of an mTOR inhibitor and a vascular endothelial growth factor inhibitor in direct comparison with each of the component agents administered as single agents, respectively, in a 3-arm study design. This study is anticipated to provide an indication of whether combination therapy in second-line treatment of metastatic RCC may provide significant advantage over single-agent therapy.

For More Information

- The phase 2 part of this study is currently enrolling patients treated with 1 prior VEGF-targeted treatment for unresectable advanced or metastatic RCC.
  - For more information, please call 1-888-422-4743 or visit http://clinicaltrials.gov/ct2/show/NCT01136733.

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