Supplementary Methods

Full Eligibility Criteria

Eligible patients were ≥18 years of age, had ECOG performance status 0-1, measurable disease per RECIST v1.1, adequate organ function, and had histologically confirmed diagnosis of locally-advanced, inoperable or metastatic RCC. Patients were not eligible if they were receiving concomitant warfarin; had any other malignancy within the past 3 years; prior cytotoxic chemotherapy, tyrosine kinase inhibitor (TKI; or other targeted anti-cancer agent), radiation therapy, or hormone therapy within 14 days or 5 half-lives (whichever is longer) prior to the first day of treatment; or immunotherapy, biologic agent, systemic steroid therapy, or unapproved investigational agent within 21 days prior to the first day of treatment. Patients were also excluded if they had unstable or inadequate cardiac function, past small bowel resection or gastric bypass surgery, major surgery within 28 days (within 3 months or unhealed surgical wounds for TelaC cohort), or untreated brain metastases or CNS disease

For the TelaE cohort, patients in dose escalation could not have >4 prior lines of therapy in the metastatic setting. For TelaE dose expansion, patients with clear cell RCC had to have received 1-3 prior treatments in the advanced/metastatic setting, including ≥1 TKI or anti-VEGF therapy. Patients with papillary RCC could not have received >3 prior treatments in the advanced/metastatic setting. For either clear cell or papillary histologies, patients with prior mTOR inhibitors (e.g., everolimus or temsirolimus) were not allowed. Patients with uncontrolled diabetes mellitus or hyperlipidemia were also excluded.

For the TelaC cohort, patients were excluded for recent or risk of hemorrhage, myocardial or cerebral infarction or other serious thromboembolic event in last 6 months, or concurrent use of strong CYP3A4 inhibitors and/or strong CYP3A4 inducers within 14 days of study entry.

Dose Adjustments

For the dose escalation part of the study, dose reductions of telaglenastat were permitted during the first 28 days in the event of a DLT. If a patient experienced a DLT, treatment continuation at a lower telaglenastat dose was permitted as long as the toxicity returned to grade ≤1 or baseline within 14 days. Patients who did not recover within 14 days were not eligible to resume treatment. Patients could miss up to 7 doses of the combination therapy during Cycle 1. Dose adjustments for everolimus or cabozantinib were permitted according to the package insert and dose reduction guidelines.

For the TelaC cohort, cabozantinib was dose reduced sequentially from starting dose of 60 mg to 40 mg, 20 mg, then discontinued for the following AEs. For grade 3 or 4 (or intolerable grade 2) hematologic toxicity, cabozantinib dose was held until resolution to grade 1 (with medical management as needed), resuming at starting dose. For grade 3 or 4 (or intolerable grade 2) diarrhea or grade 2 or 3 hypertension or palmar-plantar erythrodyesthesia syndrome, cabozantinib dose was held until resolution to grade 1 (with medical management as needed), resuming at reduced dose. For grade 3 or 4 hemorrhage, acute myocardial infarction or other arterial thromboembolic events, hypertensive crisis/severe hypertension, unmanageable fistula, gastrointestinal perforation, or reversible posterior leukoencephalopathy syndrome, both telaglenastat and cabozantinib were discontinued.

In the event of the following AEs, everolimus was dose reduced sequentially from starting dose of 10 mg QD to 5 mg, 2.5 mg, then discontinued. For grade ≥3 neutropenia or thrombocytopenia, telaglenastat and everolimus were held until resolution to grade ≤1 (or baseline), then resumed at the next lower dose level. For other grade 3 hematologic toxicities, telaglenastat and everolimus were held until resolution to grade ≤1, then resumed at the same dose level. For nonhematologic grade 2 or 3 toxicities, telaglenastat and everolimus were held until resolution to grade ≤1 (or baseline), telaglenastat was resumed at the same dose level, and everolimus at the lower dose. If toxicity recurred, then everolimus could be discontinued. For diarrhea or grade 2 or 3 stomatitis, everolimus was held until recovery to grade ≤1, then resumed at a lower dose. Telaglenastat could be held and resumed at the same or lower dose upon resolution. For metabolic events (e.g., hyperglycemia, dyslipidemia), everolimus was held until recovery to grade ≤1, then reinitiated at a lower dose. If toxicity recurred at grade 3, everolimus was discontinued. For other nonhematologic grade 3 toxicities, telaglenastat and everolimus were held until resolution to grade ≤1 (or baseline), then resumed at the same dose level. If toxicity recurred, then treatment was held and restarted at the next lower dose.