A phase II study of lenvatinib plus everolimus versus cabozantinib in patients with metastatic renal cell carcinoma (mRCC) that progressed on a PD-1/PD-L1 checkpoint inhibitor (LenCabo)

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Background

- Combinations of immune checkpoint inhibitors (ICI) and angiogenesis targeted therapy (TT) are standard first-line treatment for patients with mRCC.
- Many patients receive cabozantinib or lenvatinib + everolimus after progression on ICI combinations. These therapies were approved for treatment after progression on angiogenesis TT and have overlapping mechanisms of action with some first-line ICT combinations.
- Lenvatinib and cabozantinib have similar, but distinct, mechanisms of action, and the two agents have not been compared in a randomized clinical trial.
- *We hypothesize that lenvatinib + everolimus will produce a longer progression-free survival (PFS) compared to cabozantinib in patients with mRCC that progressed on a prior PD-1/PD-L1 checkpoint inhibitor.*

Study endpoints

Primary endpoint

- Progression-free survival

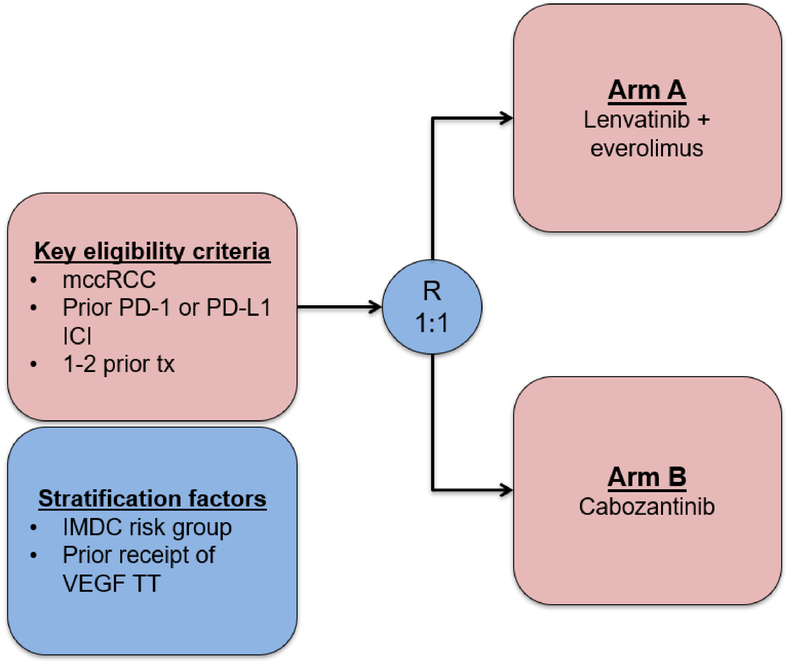
Secondary endpoints

- Objective response rate (CR + PR)
- Disease control rate (CR + PR + SD)
- Health-related quality of life (HRQOL) measured by FKSI-19, PROMIS-10, CES-D, Social Provisions Scale, and Finding Meaning in Cancer Scale.
- Safety defined as grade 3 or 4 adverse event rates
- Overall survival (OS)

Exploratory endpoints

- Assess whether alterations to *c-MET*, *AXL*, *VEGF*, *mTOR*, and *FGFR* are associated with response to treatment

Study schema



Treatment Plan

- After enrollment, 90 patients will be randomized to lenvatinib 18 milligrams (mg) daily plus everolimus 5 mg daily versus cabozantinib 60 mg daily.
- Patients will receive assigned therapy until disease progression or unacceptable treatment-related toxicity.
- Crossover is permitted.

Key eligibility criteria

Inclusion criteria	Exclusion criteria
• Histologically confirmed metastatic/advanced RCC • 1-2 prior tx in advanced setting, including progression on a PD-1/PD-L1 ICI • Measurable disease by RECIST v1.1 • Treated/stable brain mets for at least 4 weeks are permitted	• Prior lenvatinib, c-MET inhibitor, or mTOR inhibitor • Receipt of radiotherapy within 14 days or major surgery within 28 days of enrollment • Active IBD • Uncontrolled medical conditions including SBP > 140 mmHG or DBP > 90 mmHG on anti-hypertensives

Statistical planning

- PFS will be monitored using Bayesian optimal phase 2 design, and an interim analysis will be performed when 50 patients are randomized.
- The null hypothesis is that both treatment arms will produce a median PFS of 7.4 months, and the alternative hypothesis is that Arm A will produce a PFS of 12.8 months.
- Under these priors, power is 82% and the type I error rate is controlled at 0.15

Status

- LenCabo is currently enrolling at 1 site in the United States (UT MD Anderson Cancer Center).
- It will open at 2 additional US sites within the next 6 months (Moffitt Cancer Center and the University of Virginia Emily Couric Clinical Cancer Center).
- This is an investigator-initiated trial funded by Eisai (NCT05012371)

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