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LenCabo: A randomized phase II multicenter trial of lenvatinib plus everolimus (len/eve) versus (vs) cabozantinib (cabo) in patients (pts) with metastatic clear cell RCC (ccRCC) that progressed on PD-1 immune checkpoint inhibition (ICI)

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Background

First-line (1L) treatment for metastatic ccRCC consists of PD-1 ICI plus either a CTLA-4 ICI or angiogenesis targeted therapy (TT). Upon progression, many pts receive cabo or len/eve if cabo or len was not incorporated in 1L treatment. Although cabo and len share many kinase targets, lenvatinib also blocks FGFR and is paired with the mTOR inhibitor everolimus, potentially overcoming additional resistance pathways. Contemporary second-line or later (2L+) treatments have never been compared head-to-head. We hypothesized that len/eve will yield a longer PFS compared to cabo after progression on a PD-1-based ICI.

Methods

This multicenter phase II trial randomized pts with metastatic ccRCC to len 18 mg/d plus eve 5 mg/d vs cabo 60 mg/d after 1-2 prior lines of treatment, including a PD-1 ICI. Pts were stratified by IMDC risk group and prior receipt of angiogenesis TT. The primary endpoint was PFS by RECIST v1.1. Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. This trial was conducted using Bayesian optimal phase 2 (BOP2) design.

Results

90 pts were randomized, and 86 pts received at least 1 dose of assigned len/eve (n=40) or cabo (n=46). Median time from randomization to data cut-off date of August 1, 2025, was 20 months (IQR 14.9, 22.5). A total of 60 PFS events were observed. Median PFS was 15.7 months with len/eve and 10.2 months with cabo (hazard ratio 0.51, 95% CI 0.29 – 0.89, p = 0.02). The ORR was 52.6% with len/eve vs 38.6% with cabo. OS data was immature. There were no treatment-related deaths. Further safety findings will be presented.

Conclusions

Among pts with metastatic ccRCC that progressed on prior PD-1 ICIs, len/eve significantly prolonged PFS over cabo. As the first head-to-head randomized comparison of contemporary 2L+ treatments after ICI, these results are relevant to treatment sequencing and inform oncology practice.

Clinical trial identification

NCT05012371.

Legal entity responsible for the study

The authors.

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Disclosure

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