Title: *Overall survival with sequential systemic anticancer therapy and first-line response in metastatic renal cell carcinoma with ESKD: a real-world analysis*

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Background: Sequential systemic anticancer therapy (SACT) improves overall survival (OS) in mRCC, with more lines associated with longer OS. Real-world data supports ICI benefit across lines, and first-line ORR per RECIST is associated with OS.

Methods: We retrospectively included patients with mRCC and ESKD treated with VEGFR TKIs, ICIs, and/or mTOR inhibitors at the Institute of Oncology Ljubljana, Slovenia, between January 2009 and December 2025. OS was defined from cohort entry to death from any cause and censored at last known vital status or 31 December 2025. Median time to next treatment (TTNT; IQR,Range) was calculated for first-line SACT. OS was analyzed by IMDC risk group, and best response (CR, PR, SD, PD) was physician-assessed per RECIST v1.1.

Results: Among 41 patients with mRCC and ESKD, median age was 70 years; 80.5% were male, 92.7% had clear-cell histology, and 34% had favorable-risk disease (IMDC). Median SACT lines: 2 (range, 1–5). In 28 patients receiving first-line VEGFR-TKI SACT, PR was 46.4%. In 10 patients treated with first-line ICI-based therapy, PR was 50%. Of three patients receiving VEGFR-TKI plus ICI, two achieved ORR, including one CR. Overall ORR was 54% in patients treated with ICIs or ICI plus VEGFR-TKI. Median TTNT was 8 months (IQR, 3–8; range, 0–47). Median OS for all histologies across IMDC risk groups was 32 months (95% CI, 13–51). In patients receiving ≥1 ICI cycle, median OS was 47 months (95% CI, 30–63), versus 16 months (95% CI, 7–25) in those treated with VEGFR-TKIs, mTOR inhibitors, or combination SACT sequences (n=20).

Conclusion: In mRCC with ESKD, ORR with first-line ICI or ICI+VEGFR-TKI SACT was ~8% higher across IMDC groups (~34% favorable risk), with CR observed in the ICI+VEGFR-TKI group. Median OS was longer in patients receiving ≥1 ICI cycle during sequential SACT.