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Title: First-line TKI, ipilimumab–nivolumab, and lenvatinib–pembrolizumab in metastatic non–clear cell RCC: real-world survival across two UK centres

H. Maamoun [1], M. Al-Essa [2], I. Pedley [3], A. Azzabi [3], S. Grumett [2], M. Elgendy [3]

(1) Newcastle hospitals - United Kingdom, (2) Queen Elizabeth Hospital - University Hospitals Birmingham NHS Foundation Trust - United Kingdom, (3) Newcastle Hospitals - United Kingdom

Background:
The optimal first-line strategy for metastatic non clear cell RCC (nccRCC) remains unclear, with limited direct comparisons between VEGFR-TKIs, dual-immune checkpoint inhibitors, and TKI/IO combinations.

Methods:
Retrospective analysis of 41 patients treated between 2012–2025. Demographics, IMDC risk, and histology were collected. PFS was measured from therapy start to progression/death; OS from metastatic diagnosis to death/last follow-up. Kaplan–Meier medians and 95% CIs were calculated for the whole cohort and treatment specific subgroups: single-agent TKI, ipilimumab–nivolumab, and lenvatinib–pembrolizumab.

Results:
Forty one patients were included (median age 56; 56% male); IMDC: favourable 22%, intermediate 61%, poor 17%. Histologies included papillary (23/41), chromophobe (6/41), unclassified (6/41), MIT-family (5/41), and oncocytic (1/41). For the overall population, mOS was 24.15 mo (95% CI 24.38–49.41) and mPFS 13.93 mo (95% CI 16.10–49.41).
ipilimumab–nivolumab (n=6): mOS 24.38 mo (95% CI 24.38–28.81); mPFS 5.32 mo (95% CI 5.32–28.81).
lenvatinib–pembrolizumab (n=15): mOS 14.42 mo (95% CI 13.04–NR); mPFS 12.32 mo (95% CI 12.32–NR).
Single-agent TKI (n=19): mOS 24.15 mo (95% CI 18.79–49.41); mPFS 11.63 mo (95% CI 13.93–49.41).
Small cohort sizes and event sparsity contributed to wide CIs.

Conclusions:
In this real-world cohort, OS appeared similar between ipilimumab–nivolumab and single-agent TKI, whereas lenvatinib–pembrolizumab was associated with a shorter OS but the longest PFS,

approximately 12 months. The limited sample size restricts the strength and generalisability of these findings. Larger, multi-centre datasets are needed to validate regimen-level differences in first-line nccRCC.