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EAU guidelines on renal cell carcinoma: the 2025 update

Citation: Bex A, Abu Ghanem Y, Albiges L, et al. Eur Urol. 2025;87(6):683–696. doi:10.1016/j.eururo.2025.02.020. PMID: 40118739.

BACKGROUND: The EAU RCC guideline panel conducts annual structured updates of its evidence-based recommendations for the management of RCC, synthesizing new data across all disease stages and treatment modalities. Methods: A structured literature search was conducted covering May 2023 to May 2024 across Medline, EMBASE, and Cochrane Libraries, focusing on meta-analyses, systematic reviews, randomized controlled trials, and comparative retrospective studies. Evidence was synthesized using standardized EAU methodology. PubMed Key updates: Clinical practice recommendations were updated across all guideline chapters. Notable additions include new recommendations on stereotactic body radiotherapy for localized RCC, updated adjuvant therapy recommendations following KEYNOTE-564 OS data, new guidance on systemic therapy for clear-cell RCC in later lines incorporating belzutifan, updated recommendations for non-clear cell and rare subtypes, and a new dedicated chapter on hereditary RCC. Uniupo Conclusions: The guideline panel now issues a strong recommendation for adjuvant pembrolizumab following nephrectomy in intermediate- and high-risk localized ccRCC, based on the overall survival benefit demonstrated in KEYNOTE-564 (HR 0.62; 95% CI 0.44–0.87; P=0.005). ICI monotherapy or combination therapy is not recommended in patients with recurrence during or shortly after adjuvant pembrolizumab. Editorial note: The new hereditary RCC chapter and the SBRT recommendations address two areas of rapidly evolving practice. Clinicians should review the updated sequencing guidance in later-line ccRCC given the integration of belzutifan-based data.

Updated EAU recommendations on adjuvant immune checkpoint inhibitors and subsequent therapy for RCC

Citation: Bedke J, Abu Ghanem Y, Albiges L, et al. Eur Urol. 2025;87(4):491–496. doi:10.1016/j.eururo.2025.01.014. PMID: 39904712.

BACKGROUND AND FINDINGS: Following the KEYNOTE-564 trial demonstrating that adjuvant pembrolizumab significantly improved OS (HR 0.62; 95% CI 0.44–0.87; P=0.005) in localized ccRCC with high relapse risk, and the TiNivo and CONTACT-03 trials reporting results for subsequent therapy after progression on ICI therapy in the metastatic setting, the EAU RCC panel reassessed and updated its recommendations. Conclusions: A strong recommendation for adjuvant pembrolizumab was issued. ICI monotherapy or combination therapy is not recommended for patients with recurrence during or shortly after adjuvant pembrolizumab. A significant proportion of patients experience serious or life-changing side effects, which must be disclosed and discussed with patients before treatment. PubMed Editorial note: This focused update is essential reading alongside the full 2025 EAU guideline document. The explicit guidance against ICI rechallenge in patients relapsing on adjuvant pembrolizumab has direct implications for sequencing in a growing population now receiving adjuvant therapy.

FMapping heterogeneity in the tumor microenvironment of renal cell carcinoma through single-cell omics

Citation: Published January 21, 2026. UroToday Beyond the Abstract Series.

BACKGROUND: This analysis used single-cell omics approaches to map tumor microenvironment heterogeneity in RCC, providing high-resolution insights into the cellular landscape governing immune evasion and treatment response variability

across RCC subtypes. The work contributes to a growing framework for spatially resolved biomarker discovery that may inform future immunotherapy selection and resistance mechanisms. Editorial note: Single-cell omics studies in RCC are accumulating rapidly following TRACERx Renal. This work is particularly relevant in the context of this issue's focus on molecular biomarkers in small renal masses and the push toward multi-domain integrated models for patient stratification.

Durable responses to immune checkpoint inhibitor-based regimens for metastatic clear cell RCC stratified by IMDC risk groups: a pooled analysis of four randomized phase 3 trials

Citation: Jang A, Zhong JY, Kumar HLS, et al. Kidney Cancer. 2025;8(1). doi:10.1177/24684570241311419. Published January 2025; UroToday Beyond the Abstract January 12, 2026.

BACKGROUND: An ICI backbone — either ICI doublet or TKI with ICI — is the standard of care for frontline metastatic clear cell RCC. These four phase 3 trials used a sunitinib control arm, but the optimal regimen remains uncertain. This analysis aimed to compare long-term responders using extended follow-up data stratified by IMDC risk group. Sage Journals Methods: Phase 3 trial data from CheckMate 214, KEYNOTE-426, CheckMate 9ER, and CLEAR — each with a minimum follow-up of four years — was used. Pseudo individual patient data was extracted from published Kaplan-Meier curves using the IPDfromKM R package. Durable response (DR) was defined as PFS ≥24 months, extreme durable response (EDR) as PFS ≥36 months, and long-term OS as OS ≥48 months. Sage Journals Results: For the favorable risk group, lenvatinib plus pembrolizumab was associated with the highest DR (57.2%) and EDR (44.5%), while ipilimumab plus nivolumab had the lowest DR (36.0%) and cabozantinib plus nivolumab had the lowest EDR (18.8%). There was no difference in 48-month OS among regimens (p=0.11), ranging between 58.3% and 70.6%. Oxford Academic For the intermediate/poor risk group, lenvatinib plus pembrolizumab also had the highest DR and EDR, with no difference in long-term OS among regimens (p=0.22). Jefferson University Conclusions: TKI-ICI was overall associated with higher DR and EDR regardless of risk status compared to ICI doublet. Yet OS at 48 months was similar when stratified by favorable versus intermediate/poor risk. PubMed Editorial note: This pooled analysis is directly relevant to frontline treatment selection conversations. The finding that TKI-ICI combinations produce higher rates of durable and extreme durable responses — yet converge with ICI doublet on long-term OS — suggests that response depth and duration, rather than OS alone, may increasingly guide regimen choice, particularly in favorable-risk patients where treatment tolerability and quality of life carry added weight.

Effectiveness, toxicity, and treatment adjustments of lenvatinib plus pembrolizumab in advanced renal cell carcinoma: a multicenter real-world analysis

Citation: Published February 9, 2026. ESMO Open / UroToday.

BACKGROUND: Combinations of immune checkpoint inhibitors and TKIs are current standards of care in first-line treatment of patients with advanced RCC. Real-world evidence for lenvatinib plus pembrolizumab outside of clinical trial conditions remains limited, particularly for patient populations excluded from the pivotal CLEAR study. ScienceDirect Methods: A retrospective multicenter analysis evaluated the tolerability and effectiveness of lenvatinib plus pembrolizumab in 145 patients with advanced RCC treated at academic and community centers. The cohort included a higher proportion of poor IMDC risk patients (23% vs 9.3% in CLEAR), patients with ECOG PS ≥2 (14%), and non-clear cell histology (12%), all of whom were excluded from the pivotal trial. ScienceDirect Results: Adverse events occurred in 94% of patients, with fatigue (50%), hypertension (39%), and diarrhea (38%) as the most common. A large subset of patients required treatment

adjustments due to adverse events. Importantly, dose adjustments and treatment interruptions did not adversely impact outcomes. ScienceDirect Conclusions: Lenvatinib plus pembrolizumab is effective in RCC outside of clinical trials. The real-world cohort — including CLEAR-ineligible patients — supports use of this combination, though adverse events require close monitoring and proactive management with treatment adapted accordingly. ScienceDirect Editorial note: This study addresses a practical gap that every clinician faces: how the CLEAR trial's efficacy data translate to a broader, sicker, more heterogeneous population. The reassuring finding that dose reductions do not compromise outcomes is clinically actionable and supports proactive toxicity management over treatment discontinuation.Discussion: Our results suggest that cabozantinib is effective as an initial monotherapy for older patients with mRCC with a toxicity profile consistent with that reported in younger adults.

Impact of proton pump inhibitor use on the efficacy of IO-IO versus IO-TKI therapy in metastatic renal cell carcinoma

Citation: Published February 6, 2026. UroToday. Background: Proton pump inhibitors (PPIs) are among the most commonly prescribed concomitant medications in patients with metastatic RCC, given the high prevalence of gastrointestinal comorbidities and therapy-related adverse events. PPIs may impact the efficacy of both TKIs — through reduction in gastric pH affecting drug absorption and gut microbiota composition — and immune checkpoint inhibitors, with evidence suggesting immune-mediated effects on ICI outcome. However, whether this interaction differs between IO-IO and IO-TKI combination regimens has not been well characterized. PubMed Central Methods: This retrospective analysis evaluated the clinical impact of concomitant PPI use on outcomes in metastatic RCC patients receiving either an IO-IO regimen (ipilimumab plus nivolumab) or an IO-TKI combination, comparing PFS, OS, and ORR between PPI users and non-users in each treatment category. Results: PPI use significantly influenced treatment effectiveness, with worse PFS (16.3 vs 9.9 months; P<0.001) and OS (30.6 vs 18.4 months; P=0.013) observed in patients taking a PPI at treatment initiation, with the detrimental effect maintained across both treatment classes. PPI use also influenced treatment compliance, with higher rates of dose or schedule modifications and treatment interruptions in the PPI-using population. PubMed Conclusions: Concomitant PPI use is associated with inferior outcomes in metastatic RCC patients receiving ICI-based combination therapy, with the signal present in both IO-IO and IO-TKI settings. These findings reinforce the importance of careful patient selection for gastroprotective therapy and argue against indiscriminate PPI prescribing in this population. Editorial note: This is a readily actionable finding. PPIs are reflex prescriptions in oncology practice, yet this data — consistent with accumulating evidence across tumor types — suggests a meaningful clinical penalty. Reassessing PPI necessity, switching to H2 blockers where appropriate, and avoiding broad prophylactic use are low-cost interventions that may preserve treatment efficacy. Prospective validation is needed, but the signal is consistent enough to merit routine clinical attention.

CaboPoint: A Phase 2 Study of Second-line Cabozantinib After Checkpoint Inhibitor-based Combination Therapy in Patients with Metastatic Renal Cell Carcinoma.

Albiges L

Guo Z et al. World J Surg Oncol. 2025 Nov 7;23(1):421. doi: 10.1186/s12957-025-04079-4.

ackground and objective: Data are limited regarding pure second-line cabozantinib use after standard first-line checkpoint inhibitor (CPI)-based combination therapy for advanced renal cell carcinoma (aRCC). We report the final results from the prospective CaboPoint study.

Methods: The phase 2, multicentre, open-label CaboPoint

study (NCT03945773) evaluated the efficacy and safety of second-line cabozantinib in adults with aRCC, after prior ipilimumab plus nivolumab (IpiNivo; cohort A) or CPI therapy plus vascular endothelial growth factor-targeted therapy (cohort B). The primary endpoint was objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumors 1.1, evaluated by independent central review (ICR) in cohort A. The secondary endpoints included ORR by ICR in cohort B, ORR by investigator review, progression-free survival, overall survival, and safety.

Key findings and limitations: Overall, 127 patients were enrolled from 2020 to 2023 across 40 institutions. The median follow-up was 19.3 mo. ORRs (95% confidence interval [CI]) by ICR were 40.5% (29.6-52.1%) in cohort A (statistically significant and clinically meaningful) and 27.5% (14.6-43.9%) in cohort B; according to the investigator review, ORRs were 49.4% (38.4-60.5%) in cohort A and 33.3% (19.6-49.5%) in cohort B. The median (95% CI) progression-free survival was 10.9 (8.2-14.2) mo in cohort A and 8.3 (5.6-11.1) mo in cohort B. The median (95% CI) overall survival was similar between cohorts (24.3 [18.5-31.8] and 24.1 [17.1-not calculable] mo, respectively). There were no new safety concerns.

Conclusions and clinical implications: CaboPoint is the first study of pure second-line cabozantinib after first-line CPI-based combinations, providing a benchmark for future second-line aRCC studies.

FAP Expression in Renal Tumors Assessed by [(68)Ga]Ga-FAPI-46 PET Imaging and FAP Immunohistochemistry: A Case Series of Six Patients from the Prospective Exploratory Trial NCT04147494. Holzgreve

Fibroblast activation protein (FAP) has been proposed as a pan-tumor target for PET imaging using FAP-targeted tracers. Here, we explore the potential value of FAP PET in renal tumors. Methods: Six patients with renal tumors (4 with clear cell renal cell carcinoma, 1 with papillary renal cell carcinoma, and 1 with renal oncocytoma) who were included in a prospective imaging study (NCT04147494) underwent [68Ga]Ga-FAPI-46 PET before nephrectomy. FAP PET radiotracer uptake and FAP expression by immunohistochemistry were assessed in the tumors and surrounding renal parenchyma. Results: Tumoral FAP radiotracer uptake was highest in clear cell renal cell carcinoma (median SUVmax, 3.1; range, 2.5-5.3), followed by renal oncocytoma (SUVmax, 1.9) and papillary renal cell carcinoma (SUVmax, 1.1). The FAP PET signal strongly correlated with FAP expression by immunohistochemistry (SUVmax; r = 0.93; P = 0.007). Conclusion: FAP expression in different renal tumors, including renal cell carcinoma, was lower when compared with cancers with known FAP expression, such as sarcoma. Although our data do not favor FAP-based theranostic approaches in renal cell carcinoma, studies in larger cohorts are warranted for conclusive evidence.