# Highlights in Renal Cell Carcinoma from ASCO GU 2022

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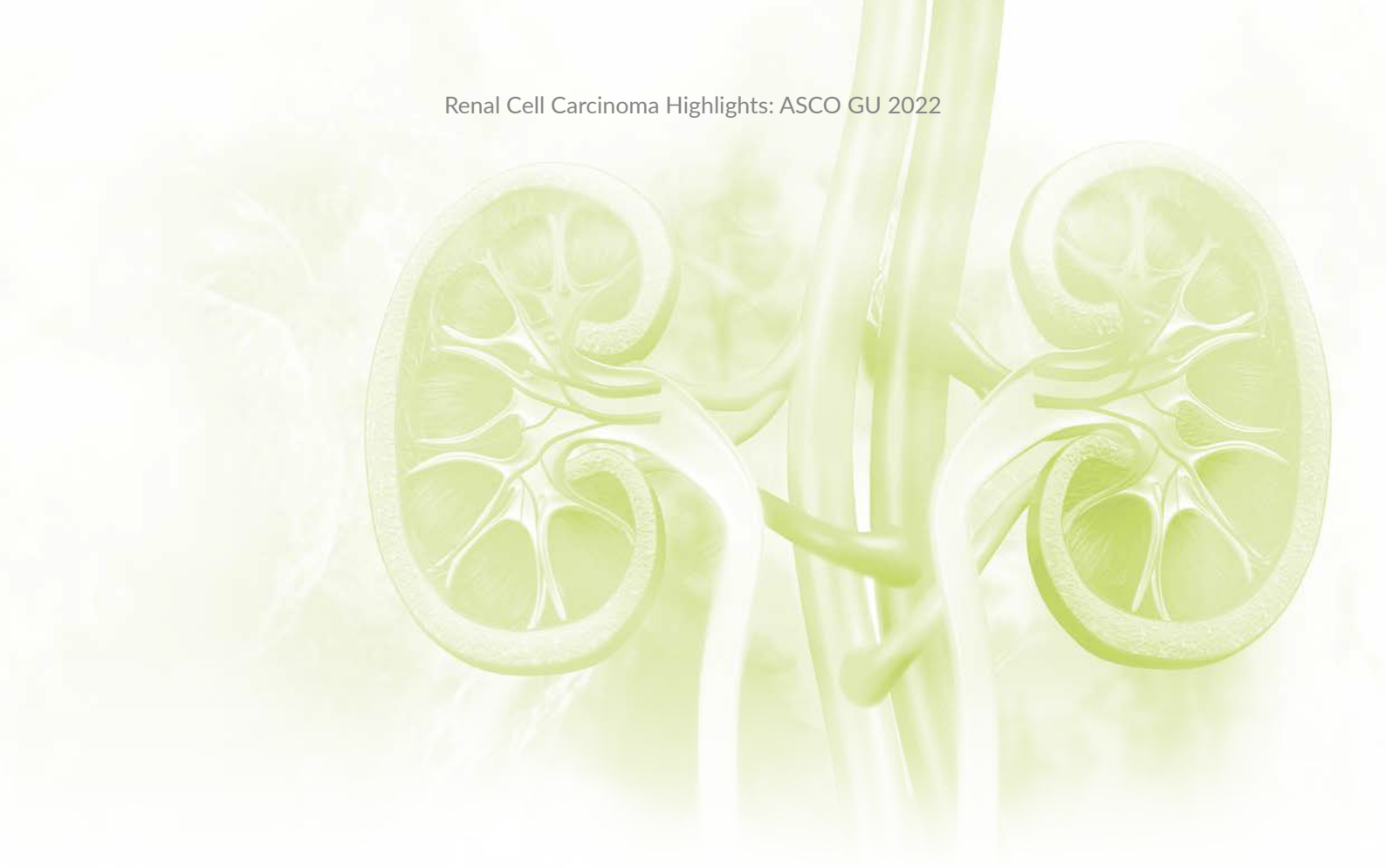
### KEYNOTE-564 30 months follow-up update: adjuvant pembrolizumab continued to improve DFS in patients with ccRCC

Based on positive results from the ongoing phase III KEYNOTE-564 trial, pembrolizumab was approved as adjuvant treatment in clear-cell renal cell carcinoma (ccRCC) by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), but not yet by Swissmedic.[1,2] This trial enrolled 994 patients with ccRCC, who met the protocol-defined criteria for intermediate-high risk, high risk or M1 no evidence of disease (NED), defined as resection of primary tumor and metastases.[3,4] Patients received either pembrolizumab (200 mg intravenously every three weeks) (n=496) or placebo (n=498) for up to one year. The primary endpoint was disease-free survival (DFS) and the secondary endpoints were overall survival (OS) and safety. Compared with data from the 24.1-month analysis presented at the 2021 ASCO Annual Meeting,[3] the updated analysis at a median follow-up of 30.1 months, which was requested by the regulatory authorities, showed a further DFS improvement with pembrolizumab versus placebo in the intention-to-treat population (HR: 0.63 [95% CI: 0.50–0.80]; p<0.0001).[4] This DFS benefit was preserved across all key subgroups, including patients with M0 disease with intermediate-high risk of recurrence (HR 0.68 [95% CI: 0.52–0.89]), M0 with a high risk of recurrence (HR: 0.60 [95% CI: 0.33–1.10]) and M1 NED (HR: 0.28 [95% CI: 0.12–0.66]). When stratified by sarcomatoid status, pembrolizumab versus placebo improved DFS in both patients with tumors without sarcomatoid features (HR: 0.63 [95% CI: 0.48–0.83]) and those with sarcomatoid features (HR: 0.54 [95% CI: 0.29–1.00]). At the data cutoff, OS data were still immature, with an HR of 0.52 (95% CI: 0.31–0.86; p=0.0048 did not cross the prespecified p-value boundary for statistical significance) after only 33% of events have occurred.[4]

Data from KEYNOTE-564 were employed in a study using a Markov model to further assess the cost-effectiveness of adjuvant pembrolizumab after nephrectomy for RCC.[5] Results of this analysis showed that at 5 years, pembrolizumab was not cost-effective for the overall trial population at current prices, but the treatment may be economical for time horizons over 15 years. However, pembrolizumab was found to be cost-effective for the highest risk subsets of RCC at 5 years.

The treatment with adjuvant pembrolizumab for patients with intermediate- or high-risk operable ccRCC was rapidly implemented in the ESMO guidelines, with a consideration that patients have to be well-informed that OS data were immature and long-term adverse events (AEs) have not yet been reported.[6] Furthermore, treatment should strictly follow the KEYNOTE-564 trial setting; therapy should be started within 12 weeks of surgery and continued for up to one year. For patients with M1 NED, systemic therapy with PD-1-based combination therapy is the standard of care for patients who relapse within one year of nephrectomy according to the ESMO guidelines.



### NeoAvAx: neoadjuvant avelumab plus axitinib provided a clinical benefit in patients with localized RCC at high risk of relapse

Current neoadjuvant approaches for patients with localized RCC are experimental and thus should not be proposed outside of clinical trials.[7] According to the ESMO guidelines, attempting to downsize venous tumor thrombus with systemic targeted therapy cannot be recommended, as there is a lack of studies showing the efficacy of this treatment strategy. Similarly, EAU guidelines underline that neoadjuvant therapy is currently under investigation and only available in clinical trials.[8]

Among trials that are assessing neoadjuvant therapy in RCC, the single-arm, phase II NEOAvAx study aimed to investigate the efficacy and safety of neoadjuvant avelumab, a programmed death-ligand 1 (PD-L1) inhibitor, in combination with axitinib, a tyrosine kinase inhibitor (TKI), in adult patients with localized RCC who are a high risk of relapse after nephrectomy.[9] This study included 40 patients with clinical high-risk, ccRCC (cT1b-4cN0-1M0, grades 3–4) who had a WHO performance status of 0–1 and no comorbidities precluding systemic therapy or surgery. Patients received avelumab (10 mg/kg intravenously every two weeks) and axitinib (5–10 mg orally twice daily), followed by surgery >36 hours after the last dose of axitinib. The primary endpoint was partial response (PR) per RECIST 1.1. in the primary tumor in ≥25% of patients. An exploratory endpoint included a biomarker analysis that evaluated the expression of PD-L1 and MHC class I, as well as the presence of CD8+, CD8+/GZMB+, CD8+/CD39+ and FoxP3+ cells. At baseline, the median patient age was 63 years and the mean tumor diameter was 10.3 cm. Results showed that downsizing occurred in most patients, with 30% of patients achieving PR in their primary tumor; the study thus met its primary endpoint. Furthermore, 32.5% of patients experienced recurrence, with a similar percentage of downsizing compared with patients without recurrence, at a median follow-up of 23.5 months. Median DFS and OS were not reached at the data cutoff. In terms of safety, surgical adverse events were as expected in this RCC patient population. Notably, high-dose corticosteroids were used in 12% of patients, but only 1 delay of nephrectomy occurred due to systemic treatment-related AEs. The exploratory analysis indicated that post-treatment tumor samples from patients with recurrence had a lower CD8+ density as compared with patients without recurrence, while pre-treatment biopsies showed no differences.

### CheckMate 9ER: the final OS analysis showed a persistent survival benefit with nivolumab plus cabozantinib in patients with advanced RCC

Both the ESMO and the EUA guidelines recommend various combinations of immune checkpoint inhibitors and TKIs for the treatment of advanced ccRCC, including pembrolizumab plus lenvatinib, pembrolizumab plus axitinib and nivolumab plus cabozantinib, irrespective of International Metastatic RCC Database Consortium (IMDC) risk groups.[6,8] In addition,

ipilimumab plus nivolumab are recommended for first-line treatment of IMDC intermediate- and poor-risk disease. Of these treatment regimes, only pembrolizumab plus lenvatinib are not yet registered in Switzerland.[6,8,10,11]

The approval of nivolumab plus cabozantinib for the treatment of previously untreated patients with advanced or metastatic ccRCC was based on data from the phase III CheckMate 9ER trial, demonstrating the superiority of nivolumab plus cabozantinib to sunitinib in this patient population.[11] In the final OS analysis presented at the 2022 ASCO Genitourinary Cancers Symposium, the median OS was 37.7 months in the nivolumab plus cabozantinib arm and 34.3 months in the sunitinib arm at a median follow-up of 32.9 months, translating into a 30% reduction in the risk of death (HR: 0.70 [95% CI: 0.55–0.90]).[12] The median progression-free survival (PFS) was doubled with nivolumab plus cabozantinib (16.6 months vs 8.3 months; HR: 0.56 [95% CI: 0.46–0.68]). Most importantly, this frontline combination therapy achieved an overall response in more than half of the patients (55.7% and 28.4% with sunitinib), with a complete response rate of 12.4%. Notably, only 6.2% of patients receiving nivolumab and cabozantinib experienced progressive disease. These results underline the efficacy of this treatment combination, especially important for treatment-naïve patients whose disease should not progress due to critical locations of metastases. An exploratory post hoc analysis further showed a benefit of nivolumab plus cabozantinib at target lesions across all assessed organ sites. No new safety signals were reported.

Another presentation reported results of health-related quality of life (HRQoL) analysis of patients enrolled in CheckMate 9ER.[13] At 3 years, nivolumab plus cabozantinib were associated with improved HRQoL compared with sunitinib, with no decline in scores for functional assessment of cancer therapy-kidney symptom index (FKSI-19) and EQ-5D-3L domains. Patients treated with nivolumab plus cabozantinib versus sunitinib also showed decreased odds of being bothered by treatment side effects. Limitations of this analysis include the open-label nature of the trial as well as the different administration routes and schedules for the therapies.

The same research group also presented HRQoL data in treatment-naïve patients with advanced RCC who were treated with either nivolumab plus ipilimumab or sunitinib in the phase III Checkmate 214.[14] At a 5-year follow-up, nivolumab plus ipilimumab versus sunitinib showed HRQoL benefits, with reduced risk of deterioration in HRQoL and reduced disease-related symptoms in patients with advanced RCC.

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**9.** Bex A, Abu-Ghanem Y, Van Thienen JV, et al. Efficacy, safety, and biomarker analysis of neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). Presented at: 2022 ASCO Genitourinary Cancers Symposium; 17–19 February 2022. San Francisco, CA, USA. Oral presentation 289.
**10.** Keytruda® (pembrolizumab). Product information. Swissmedic 2021. [Accessed March 2022]. Available from: https://www.swissmedicinfo.ch.
**11.** OPDIVO® (nivolumab). Product information. Swissmedic 2022. [Accessed March 2022]. Available from: https://www.swissmedicinfo.ch.
**12.** Powles T, Choueiri TK, Burotto M, et al. Final overall survival analysis and organ-specific target lesion assessments with two-year follow-up in CheckMate 9ER: Nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. Presented at: 2022 ASCO Genitourinary Cancers Symposium; 17–19 February 2022. San Francisco, CA, USA. Poster F12.
**13.** Cella D, Motzer RJ, Blum SI, et al. Health-related quality of life (HRQoL) in previously untreated patients with advanced renal cell carcinoma (aRCC): CheckMate 9ER updated results. Presented at: 2022 ASCO Genitourinary Cancers Symposium; 17–19 February 2022. San Francisco, CA, USA. Poster E10.
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