

## Meeting Report

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# EAU 2022 Highlights on Renal Cell Carcinoma

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The most debated topic on renal cell carcinoma (RCC) during the EAU 2022 in Amsterdam was the 30 month follow-up update of the Keynote-564 trial. In this trial patients with intermediate and high risk for recurrence after nephrectomy with curative intent, and with no evidence of disease at the time of inclusion were randomized between adjuvant treatment with pembrolizumab for 1 year or placebo. A small group of patients with M1 disease who underwent metastasectomy were also included. In the intermediate risk (pT2 with Grade 4 or sarcomatoid differentiation, N0, M0; pT3, any grade, N0, M0), the high risk (T4, any grade, N0, M0; any pT, any grade, N+, M0) and M1 (no evidence of disease after surgery) groups disease-free survival was better with pembrolizumab compared with placebo (HR 0.63 [95% CI 0.50–0.80]). Although the median disease-free survival was not reached in any of the groups, the estimated number of participants alive and disease free after 30 months was 75.2% (95% CI 70.8–79.1) in the pembrolizumab group and 65.5% (60.9–69.7) in the placebo group [1].

Despite these positive findings the study was much debated during several highlight sessions. The survival benefit for the intermediate risk group is less compared to the high risk and M1 groups. This was especially true for those patients with a moder-

ate expected advantage of adjuvant therapy, 22% of whom had treatment discontinued due to an adverse event, which should be taken into account. Also, the high costs of the adjuvant treatment should be kept in mind.

One presented abstract evaluated the natural history of a cohort of patients similar to the groups included in the Keynote 564 trial, with heterogeneous disease stages which exhibited different natural histories. The question was raised as to whether all patients should be offered adjuvant treatment [2].

Another abstract compared a real life cohort to the placebo arm of the Keynote 564 study with the aim of identifying those patients who may benefit most from adjuvant Pembrolizumab. Different baseline characteristics, pathological features, and early recurrence outcomes rates were found in the real life cohort compared with the placebo arm of the Keynote 564 study. The authors suggest that this highlights the need for proper patient selection and state that tumor necrosis, lymph vascular invasion and positive nodes may be more accurate risk factors for stratification [3].

Nonetheless the most recent EAU guidelines now recommend offering adjuvant pembrolizumab to patient groups as defined in the study. However, the recommendation is not made for the M1 patient group as they are considered a different entity. While we await overall survival data the basis for the recommendation remains weak [4].

Many abstracts presented showed improvements in techniques to lower or even fully avoid ischemia

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time during partial nephrectomy. The importance of avoiding end stage renal disease (ESRD) was pointed in one of the abstract sessions. ESRD occurs 10 times more often in patients who undergo surgery for RCC. Patients with ESRD have survival rates < 50% compared to a control group. Important risk factors for developing ESRD are undergoing a radical instead of partial nephrectomy, male sex, higher T stadium, diabetes, hypertension and presence of chronic kidney disease before surgery [5]. The relative importance of ischemia time during partial nephrectomy was shown in one study evaluating results of 1140 partial nephrectomies. It was found that the length of the ischemia time did not influence the renal function at 6 months follow up nor the chance of survival. However, ischemia time was inversely correlated with a chance of significant blood loss [6]. Another study investigated factors that were associated with a  $\geq 5\%$  increase in function of the unaffected kidney after partial nephrectomy evaluated by a MAG 3 scan. A tumor diameter  $\geq 3$  cm and a warm ischemia time  $\geq 25$  minutes resulted in an increase  $\geq 5\%$  of the unaffected kidney [7]. For clinical use: the previously developed Martini nomogram (including gender, Charlson comorbidity index, pre-operative eGFR, R.E.N.A.L. score, and postoperative acute kidney injury) to predict significant (>25%) renal function decline after partial nephrectomy was validated [8].

For RCC imaging the clinical performance of Technetium-99 m ( $^{99m}\text{Tc}$ ) –sestamibi SPECT/CT to differentiate oncocyctic tumors from RCC was evaluated. Because of a negative predictive value of 82.5% for ruling out oncocyctic tumor for masses that underwent pathologic sampling, this scan is not ready for routine clinical use or to replace a renal mass biopsy [9]. Zirconium-89 ( $^{89}\text{Zr}$ )-girentuximab PET/CT is a promising tool to noninvasively differentiate clear cell RCC from non-clear cell RCC. Data on the safety, biodistribution and radiation dose of  $^{89}\text{Zr}$ -girentuximab, which was necessary to initiate the multi-center phase III study on  $^{89}\text{Zr}$ -girentuximab PET/CT (ZIRCON), was presented [10].

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## AUTHOR CONTRIBUTIONS

- TO and PM both made substantial contributions to the work.
- TO and PM both involved in writing the article.
- TO and PM both approved the final version to be published.
- TO and PM both agreed to be accountable for the accuracy and integrity of the work.

## CONFLICTS OF INTEREST

Tim van Oostenbrugge has no conflicts of interest to declare.

Peter Mulders is an Editorial Board Member of this journal, but was not involved in the peer review process of this paper, nor had access to any information regarding its peer-review.

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