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Brief Correspondence

2021 Updated European Association of Urology Guidelines on the Use of Adjuvant Pembrolizumab for Renal Cell Carcinoma

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Abstract

Adjuvant treatment of nonmetastatic high-risk renal cell carcinoma is an unmet medical need. In the past, several tyrosine kinase inhibitor trials have failed to demonstrate an improvement of disease-free survival (DFS) in this setting. Only one trial (S-TRAC) provided evidence for improved DFS with sunitinib but without an overall survival (OS) signal. Keynote-564 is the first trial of an immune checkpoint inhibitor that significantly improved DFS with adjuvant pembrolizumab, a programmed death receptor-1 antibody, in clear cell renal cell carcinoma with a high risk of relapse. The intention-to-treat population, which included a group of patients after metastasectomy and no evidence of disease (M1 NED), had a significant DFS benefit. The OS data are not mature as yet. The Renal Cell Carcinoma Guideline Panel issues a weak recommendation for the adjuvant use of pembrolizumab for high-risk clear cell renal carcinoma, as defined by the trial until final OS data are available. However, the trial reilluminates the discussion on when and in whom metastasectomy should be performed. Here, caution is necessary not to perform metastasectomy in patients with poor prognostic features and rapid progressive disease, which must be excluded by a confirmatory scan of disease status prior to planned metastasectomy.

Patient summary: New data from the adjuvant immune checkpoint inhibitor trial with pembrolizumab (a programmed death receptor-1 antibody) for the treatment of high-risk clear cell renal cell carcinoma (ccRCC) after surgery showed that the drug prolonged

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the period of being cancer free significantly, although whether it prolonged survival remained uncertain. Consequently, pembrolizumab is cautiously recommended as additional (ie, adjuvant) treatment in high-risk ccRCC after kidney cancer surgery.

Immune checkpoint inhibitors (ICIs), designed to restore and enhance immune activity against cancer cells, have shown impressive efficacy in advanced renal cell carcinoma (RCC) [1–5]. Several randomised phase III trials of adjuvant ICIs are on-going, and the Keynote-564 trial is the first to report results (Table 1) [6]. A meta-analysis of previous adjuvant vascular endothelial growth factor receptor (VEGFR)-targeted therapy trials has not demonstrated unequivocal disease-free survival (DFS) or overall survival (OS) benefits for patients with high-risk RCC after nephrectomy, and it is neither recommended by the European Association of Urology (EAU) guidelines nor approved by the European Medicines Agency, despite initial enthusiasm [7–9].

Table 2 – Updated EAU RCC guideline recommendation for the adjuvant use of ICIs in high-risk RCC

Recommendations	Strength rating

After surgery with curative intent, offer adjuvant pembrolizumab to ccRCC patients with a recurrence risk as defined in the Keynote-564 trial:
• Intermediate-high risk:
  • pT2, grade 4 or sarcomatoid, N0 M0
  • pT3, any grade, N0, M0
• High risk:
  • pT4, any grade, N0, M0
  • Any pT, any grade, N+, M0
• M1 NED:
  • NED after resection of oligometastatic sites ≤1 yr from nephrectomy
	Weak

Perform a confirmatory axial scan of disease status prior to metastasectomy to rule out rapid progressive metastatic disease that requires systemic treatment	Weak

ccRCC = clear cell renal cell carcinoma; EAU = European Association of Urology; ICI = immune checkpoint inhibitor; NED = no evidence of disease; RCC = renal cell carcinoma.

Adjuvant treatment in high-risk RCC

The Keynote-564 phase III trial is the first adjuvant ICI trial to report positive primary endpoint data on DFS [6]. Keynote-564 evaluated pembrolizumab (17 cycles of 3-weekly therapy) versus placebo as adjuvant therapy for 994 patients with intermediate-risk (pT2, grade 4 or sarcomatoid, N0 M0; or pT3, any grade, N0, M0), high-risk (pT4, any grade, N0 M0; or pT any stage, and grade, or N+, M0), or M1 (no evidence of disease [NED] after primary tumour plus soft tissue metastases completely resected ≤1 yr from nephrectomy) disease (Table 2). The median follow-up, defined as the time from randomisation to data cut-off, was 24.1 mo. The primary endpoint of DFS per investigator assessment was significantly improved in the pembrolizumab group versus the placebo group (hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.53–0.87, p = 0.001). The estimated 24-mo DFS rate was 77% versus 68% for pembrolizumab versus placebo. Benefit occurred across broad subgroups of patients including those with M1/NED disease after surgery (n = 58 [6%]). Investigator-assessed DFS was considered preferable to DFS by central review due to its clinical applicability. OS showed a nonstatistically significant trend towards a benefit in the pembrolizumab arm (HR 0.54, 95% CI 0.30–0.96, p = 0.0164). Follow-up was short and few OS events occurred (2-yr OS rate of 97% [pembrolizumab] vs 94% [placebo]). Grade 3–5 all-cause adverse events occurred in 32% versus 18% of patients for pembrolizumab versus placebo. Quality of life assessment by FKSI-DRS and QLQ30 did not show a statistically significant or clinically meaningful deterioration in

Table 1 – Updated EAU RCC guideline recommendation for the adjuvant treatment of high-risk ccRCC.

Phase III trial of PD-1 immune checkpoint inhibitors in adjuvant RCC						
Study	*N*	Experimental arm	Primary endpoint	Risk groups	DFS (mo) Median (95% CI) HR	OS (mo) Median (95% CI) HR
Keynote-564 **NCT03142334** Median follow-up of 24.1 mo [6]	994	Pembrolizumab 200 mg IV Q3W (17 cycles) vs placebo	DFS in the ITT by IR	**Intermediate-high:** pT2 grade 4 or sarcomatoid; pT3 any grade	ITT: Pembro: NR (NE) Placebo: NR (NE)	ITT: Pembro: NR (NE) Placebo: NR (NE)
				High: pT4 any grade, pN1	HR: 0.68 (95% CI: 0.53–0.87) *P* < 0.002	HR: 0.54 (95% CI: 0.30–0.96) Not significant
				M1 NED: cM0 after resection of oligometastatic disease <12 mo	DFS at 24 mo: Pembro: 77.3% Placebo: 68.1%	Alive at 24 mo: Pembro: 96.6% Placebo: 93.5%

CI = confidence interval; HR = hazard ratio; IR = investigator review; ITT = intention-to-treat; IV = intravenous; mo = months; NE = non-estimable; NR = not reached; OS = overall survival; PD-1 = programmed death-receptor 1; PEMBRO = pembrolizumab; PFS = profession-free survival; Q3W = every 3 weeks.

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health-related quality of life or symptom scores for either adjuvant pembrolizumab or placebo.

After quality of evidence and strength of recommendation assessment using a modified GRADE approach, the EAU RCC Guideline Panel reached consensus and issued a weak recommendation for adjuvant pembrolizumab for patients with high-risk (defined as per study) operable clear-cell renal cell cancer (ccRCC; Supplementary material), at least until the final OS data are available. The panel included a patient questionnaire and a poll among their guideline members prior to Kyenote-564 data release in their assessment of the harms and benefits (Supplementary material). Although the EAU guideline previously did not recommend sunitinib despite positive DFS data in the absence of OS benefit [10–12], the panel decided to recommend adjuvant pembrolizumab for the following reasons:

1. ICI therapy has a different mode of action than VEGFR tyrosine kinase inhibitor (TKI), resulting in complete responses in up to 16% of patients in programmed death receptor-1 (PD-1) unselected populations in metastatic disease [3].
2. Despite immature OS data with the early OS signal potentially driven by the M1 population, the panel cannot exclude that a survival benefit will emerge. This was not the case in the adjuvant sunitinib trial (STRAC) [6,12].
3. Pembrolizumab is better tolerated than sunitinib and does not lead to a decline of quality of life compared with placebo, unlike sunitinib [6,13].
4. A number of adjuvant VEGFR trials failed to show a DFS advantage for sunitinib or other VEGFR inhibitors, resulting in a negative meta-analysis [9].

The panel considered the following cautionary points in their decision, which led to a weak recommendation:

1. A high proportion of patients, cured by surgery, are receiving unnecessary and potentially harmful treatment.
2. The tolerability profile is acceptable, but grade 3–5 adverse events were 14.7% higher in the pembrolizumab arm (32.4%) than in the placebo arm (17.7%, all cause). Approximately 18% of patients required treatment discontinuation early for adverse events, which provides a broad indicator of tolerability. Endocrine adverse events may require lifelong therapy.
3. Other ICI trials have not yet been reported and are not available for meta-analysis.
4. Biomarker analyses to predict outcome and adverse events are not available.
5. Final OS data are not yet available.

Metastasectomy and subsequent systemic treatment in M1 NED

The panel acknowledges that the trial needs to be assessed based on its original design, which includes a small percentage of patients who underwent complete metastasectomy (6% in the experimental arm and 6% in the placebo arm). However, in Kyenote-564, patients in the M1 NED cohort had metastasectomy within 1 yr after primary diagnosis. A metachronous interval of <1 yr for recurrences following surgery with curative intent is a poor prognostic factor [14]. Systemic therapy based on immune combinations has stronger levels of evidence than surgery in this advanced disease setting [15]. In addition, TKI-driven adjuvant trials after metastasectomy have shown no DFS or OS benefit [16,17].

Results for single-agent pembrolizumab after surgery for metastatic disease are therefore difficult to interpret due to the small subgroup. Nevertheless, the DFS HR of 0.29 (95% CI 0.12–0.69) in favour of resection of M1 to NED plus pembrolizumab shows that patients with subclinical but progressive disease who were subjected to metastasectomy had a benefit of adjuvant systemic therapy with pembrolizumab. Based on the current data, it cannot be concluded that for patients with oligoprogressive disease, metastasectomy within the 1st year of initial diagnosis of the primary and subsequent adjuvant pembrolizumab is superior to a period of observation and dual immunotherapy-based combination first-line therapy upon progression. Data from the TKI era suggest that patients with metastatic disease recurrence can be observed for up to a median of 16 mo before systemic therapy is required and that this practice is common in real-world settings (30%) [18,19].

In addition, it is possible that metastasectomy may lead to poorer outcomes compared with systemic therapy approaches as a relapse within the first 12 mo and presentation with synchronous (oligo-) metastatic disease is attributed to the International Metastatic RCC Database Consortium intermediate-risk group [20]. The panel therefore does not encourage metastasectomy and adjuvant pembrolizumab in this advanced population within 1 yr after primary surgery. A careful reassessment of disease status to rule out rapid progressive disease should be performed. Data from other adjuvant ICI studies including M1 NED subgroups may clarify this issue further (IMmotion010, NCT03024996).

Conclusion

Keynote-564 is the first trial to demonstrate improved DFS in ccRCC patients in the adjuvant setting. OS is still immature. Further trials that have unreported results are currently on-going in this setting (IMmotion010, NCT03024996; CheckMate-914, NCT03138512; RAMPART, NCT03288532; and PROSPER RCC, NCT03055013).

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Study concept and design: Bedke, Powles, Ljungberg, Bex.
Acquisition of data: Bedke, Bex.
Analysis and interpretation of data: Bedke, Powles, Bex.
Drafting of the manuscript: Bedke, Bex.
Critical revision of the manuscript for important intellectual content: Albiges, Capitanio, Giles, Hora, Lam, Ljungberg, Marconi, Klatte, Volpe, Abu-Ghanem, Dabestani, Fernández-Pello, Hofmann, Kuusk, Tahbaz.
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