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European Association of Urology

EAU Guidelines View

Updated European Association of Urology Guidelines on the Use of Adjuvant Immune Checkpoint Inhibitors and Subsequent Therapy for Renal Cell Carcinoma

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Abstract

The KEYNOTE-564 trial showed that adjuvant immune checkpoint inhibitor (ICI) therapy with pembrolizumab, a PD-1 antibody, significantly improved disease-free survival (DFS) and overall (OS) survival in localised clear-cell renal cell carcinoma (RCC) with a high risk of relapse. The TiNivo and CONTACT-03 trials have reported results for subsequent therapy after progression on ICI therapy in the metastatic setting. The European Association of Urology (EAU) RCC guidelines panel reassessed the new trial results to update recommendations for adjuvant therapy and post-adjuvant therapy. Adjuvant pembrolizumab significantly improved OS (hazard ratio 0.62, 95% confidence interval 0.44–0.87; $p = 0.005$). Recent trials of subsequent ICI after recurrence on ICI in the metastatic setting do not support ICI monotherapy or combination therapy in patients with recurrence on or after adjuvant ICI therapy. There are no prospective trial results for treatment after adjuvant pembrolizumab failure. On the basis of the recent results, the

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High risk
Metastasectomy
Clear cell histology
Renal cell carcinoma

EAU RCC guidelines panel has updated the recommendation for adjuvant therapy and now issues a strong recommendation for adjuvant pembrolizumab. ICI monotherapy or combination therapy is not recommended in patients with recurrence during or shortly after adjuvant pembrolizumab.

Patient summary: Treatment with an immunotherapy drug called pembrolizumab after surgery in patients with intermediate-risk or high-risk kidney cancer delays the time to recurrence of cancer and prolongs survival. Therefore, pembrolizumab after surgery is strongly recommended for these patients. However, a significant proportion of patients have life-changing or serious side effects and these must be discussed.

1. Introduction

In 2022, the European Association of Urology guideline on renal cell carcinoma (RCC) included a weak recommendation for pembrolizumab, an immune checkpoint inhibitor (ICI) against PD-1, as adjuvant therapy in patients with intermediate or high risk of recurrence following (partial) nephrectomy [1]. Initially, the panel considered several caveats in their decision to recommend pembrolizumab: This included the lack of mature or significant overall survival (OS) data. The lack of biomarkers for patient selection to avoid overtreatment, and the absence of results from other ongoing ICI adjuvant trials were also considered [2]. Recent data with longer follow-up now show a significant OS signal for adjuvant pembrolizumab, prompting this update. Other trials have also reported negative results in this setting and are covered in this guideline update (Table 1) [3–7]. We also consider standard treatment after adjuvant pembrolizumab and the role of ICI rechallenge.

2. New evidence for adjuvant ICI treatment

2.1. *KEYNOTE-564 update on OS*

KEYNOTE-564 evaluated pembrolizumab (17 cycles of 3-weekly therapy) versus placebo as adjuvant therapy for 994 patients with clear-cell RCC with intermediate-high risk (pT2, grade 4 or sarcomatoid differentiation, N0 M0; or pT3, any grade, N0, M0) or high risk (pT4, any grade, N0 M0; or pT any stage, and grade, or N+, M0), or M1 disease (no evidence of disease [NED] after complete resection of the primary tumour plus soft-tissue metastases $\leq$1 yr from nephrectomy). The disease-free survival (DFS) data have been reported and updated at 30.1-mo follow-up and the panel issued recommendations on pembrolizumab use in 2021 and 2022 [1,2].

At 57.2 mo, 141 deaths (70.5% of the planned events) had occurred in KEYNOTE-564 (55 in the pembrolizumab arm, 86 in the placebo arm), triggering the third protocol-specified interim analysis [4]. The results represented a significant improvement in OS favouring pembrolizumab (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.44–0.87; p = 0.002). At 48 mo, the net survival difference between the experimental arm (91.2% alive) and the placebo arm (86% alive) was 5.1%. In an exploratory subgroup analysis, the benefit was observed across all risk groups (intermediate-high risk, high risk, and M1 NED). The updated investigator-assessed DFS in the intention-to-treat population demonstrated a HR of 0.72 (95% CI 0.59–0.87) in favour of pembrolizumab at median follow-up of 57.2 mo. There were no new safety signals: 91 patients (18.6%) in the experimental arm versus six (1.2%) in the placebo arm experienced grade 3–4 treatment-related events. Quality of life (QoL) assessment using the Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index-Disease-Related Symptoms (FKSI-DRS) and European Organisation for Research and Treatment of Cancer QoL Questionnaire-Core 30 (QLQ-C30) instruments did not show a statistically significant or clinically meaningful deterioration in health-related QoL or symptom scores for either adjuvant pembrolizumab or placebo [8]. Concerns were raised by the guideline committee that the tools used to assess QoL in this setting may not have been appropriate, as patients with life-changing toxicity would clearly have an altered QoL in comparison to those who were not affected. Regarding subsequent therapies, 128/161 patients (79.5%) in the pembrolizumab arm and 171/210 (81.4%) in the placebo arm received some form of subsequent treatment, included systemic anticancer drug therapy, radiation therapy, or further surgery. Among the participants who received any systemic therapy, 42/102 patients (41.2%) in the pembrolizumab arm and 101/145 (69.7%) in the placebo arm received PD-1/PD-L1 ICIs [4].

2.2. *Checkmate-914: nivolumab monotherapy*

The phase 3 CheckMate 914 trial (NCT03138512) investigated clinical outcomes for 6 mo of adjuvant nivolumab + ipilimumab (parts A and B) and nivolumab monotherapy (part B) for patients with surgically resected stage II/III clear-cell RCC with a high risk of relapse. Results for part A showed no DFS benefit for adjuvant nivolumab plus ipilimumab versus placebo in the overall study population at median follow-up of 37.0 mo (interquartile range 31.3–43.7) [6].

Results for part B, which investigated the contribution of components for part A and the efficacy and safety of nivolumab monotherapy versus placebo in this setting, were reported at the 2024 genitourinary meeting of the American Society of Clinical Oncology [5]. Following a protocol amendment, part B was added to complement part A to allow comparison of nivolumab monotherapy to nivolumab + ipilimumab and evaluation of the potential benefits of

Table 1 – Results from phase 3 trials of adjuvant PD-1 immune checkpoint inhibitor therapy in RCC

Study	Pts	Experimental arm	Primary endpoint [a]	Risk groups	Median DFS, mo (95% CI) [a]	Median OS, mo (95% CI) [a]
KEYNOTE-564 NCT03142334 Median follow-up 57.2 mo [4,8]	994	Pembro 200 mg IV Q3W (17 cycles) vs placebo	DFS by IR	Intermediate-high:pT2 G4 or SMD; pT3 any grade High: pT4 any grade, pN1 M1 NED: cM0 after ROMD <12 mo	Pembro: NR (NE) Pbo: NR (NE) HR 0.72 (95% CI 0.59–0.87); $p < 0.002$ [b] 48-mo DFS rate: Pembro 64.9% vs Pbo 56.6%	Pembro: NR (NE) Pbo: NR (NE) HR 0.62 (95% CI 0.44–0.87); $p = 0.005$ Alive at 48 mo: Pembro 91.2% vs Pbo 86.0%
IMmotion010 NCT03024996 Median follow-up 44.7 mo [7]	778	Atezo 1200 mg IV Q3W (16 cycles or 1 yr) vs Pbo	DFS by IR	By TNM status: pT2 G4 or SMD; pT3a G3–4; pT3b/c/T4 any grade, pN1 M1 NED: cM0 after ROMD (synchronous or ≥12 mo)	Atezo: 57.2 (44.6–NE) Pbo: 49.5 (47.4–NE) HR 0.93 (95% CI 0.75–1.15); $p = 0.4950$ DFS at 24 mo: NR	Atezo: NE (59.8–NE) Pbo: NE (NE–NE) HR 0.97 (95% CI 0.67–1.42) Alive at 24 mo: NR
CheckMate 914 NCT03138512						
Part A Median follow-up 37.0 mo [6]	816	Nivo 240 mg IV Q2W (12 cycles) + ipilimumab 1 mg/kg IV Q6W (4 cycles) vs Pbo	DFS by BICR	By TNM status: pT2a G3–4; pT2b/T3/T4 any grade, pN1	Nivo + Ipi: NR (NE) Pbo: 50.7 (48.1–NE) HR 0.92 (95% CI 0.71–1.19); $p = 0.5347$ 24-mo DFS rate: Nivo + Ipi: 76.4% vs Pbo: 74.0%	NR
Part B Median follow-up 18.7 mo [5]	825	Nivo 240 mg IV Q2W (12 cycles) + Pbo Q6W (4 doses) vs Pbo IV Q2W (12 doses) + Pbo IV Q6W (4 doses) vs Nivo 240 mg IV Q2W (12 cycles) + Ipi 1 mg/kg IV Q6W (4 cycles) 2:1:1	DFS by BICR	By TNM status: pT2a G3–4; pT2b/T3/T4 any grade, pN1	Nivo NR (NE) vs Pbo: NR (NE) HR 0.87 (95% CI 0.62–1.21); $p = 0.3962$ 18-mo DFS rate: Nivo 78.4% vs Pbo 75.4% **Secondary endpoint** Nivo: NR (NE) Nivo + Ipi: NR (NE) HR 1.27 (95% CI 0.92–1.76) 18-mo DFS rate: Nivo 78.4% vs Nivo + Ipi: 72.3%	NR
PROSPER NCT03055013 Median follow-up 30.4 mo [3]	779	NeoA Nivo 240 mg IV Q2W (2 cycles), then adjuvant Nivo 240 mg Q2W for 3 mo and Q4W for 6 mo vs Obs	RFS by IR	By TNM status: ≥cT2 (7 cm) or cT any cN1	**Recurrence-free survival** Nivo NR (NE) vs Obs: NR (NE) HR 0.94 (95% CI 0.74–1.21); $p = 0.32$	Nivo: NR (NE) Obs: NR (NE) HR 1.28 (95% CI 0.84–1.95); $p = 0.26$

Atezo = atezolimumb; BICR = blinded independent central review; CI = confidence interval; DFS = disease-free survival; G = grade; HR = hazard ratio; Ipi = ipilimumab; IR = investigator review; IV = intravenous; NED = no evidence of disease; NE = not estimable; NeoA = neoadjuvant; Nivo = nivolimumab; NR = not reached; Obs = observation; OS = overall survival; Pbo = placebo; Pts = patients; Q2W/3W/4W/6W = every 2/3/4/ 6 wk; ROMD = resection of oligometastatic disease; SMD = sarcomatoid differentiation.

[a] Results for the intention-to-treat population.

[b] From first interim analysis at 24 mo.

adjuvant nivolumab monotherapy versus placebo. After minimum follow-up of 18.0 mo, the target of 149 DFS events had occurred, which provided 60% power for detecting a HR of 0.68 at $\alpha = 0.05$ (two-sided) for the primary endpoint of DFS in a cohort of approximately 600 patients randomised to the nivolumab and placebo arms. Patients were randomised 2:1:1 to nivolumab (n = 411), placebo (n = 208), or nivolumab + ipilimumab (n = 206). Patient and tumour characteristics were well balanced.

The primary endpoint of DFS with nivolumab versus placebo according to blinded independent central review was not met (HR 0.87, 95% CI 0.62–1.21; p = 0.4); median DFS was not reached in either arm. Selected exploratory subgroup analyses by sarcomatoid features (HR 0.42, 95% CI 0.17–1.07) and haemoglobin below the lower limit of normal (HR 0.49, 95% CI 0.25–0.95) favoured nivolumab in comparison to placebo. Investigator-assessed DFS revealed no significant difference between nivolumab and placebo (HR 0.80, 95% CI 0.58–1.12; p = 0.2). The safety of nivolumab monotherapy in this population was consistent with its known profile in advanced RCC: 45 patients (11%) in the nivolumab arm, six (3%) in the placebo arm, and 63 (31%) in the nivolumab + ipilimumab arm discontinued treatment because of study drug toxicity. These results do not support the use of adjuvant nivolumab in patients with surgically resected stage II/III clear-cell RCC with a high risk of relapse and are in line with data previously reported for the PROSPER trial.

There have been no further updates for IMmotion010 or CheckMate 914 arm A. The perioperative PROSPER trial showed that preoperative and postoperative nivolumab in comparison to surgery alone did not improve recurrence-free survival (HR 0.94, 95% CI 0.74–1.21; one-sided p = 0·32) at median follow-up of 30.4 mo [3].

3. Summary

3.1. *Adjuvant pembrolizumab*

The panel reached consensus and issues a strong recommendation for adjuvant pembrolizumab after surgery for patients with intermediate-high risk or high risk clear-cell RCC or M1 NED disease as defined in KEYNOTE-564, as final OS data are now available, with no deterioration in QoL according to the evaluable evidence (Table 2 and Supplementary Table 1) [4,8,9].

The panel recommends adjuvant pembrolizumab, but the following general topics should be considered in the adjuvant setting:

- A proportion of patients who are cured by surgery are receiving unnecessary treatment.
- The tolerability profile is acceptable, but the rate of grade III–V treatment-related adverse events was 18.6% in the pembrolizumab arm versus just 1.2% in the placebo arm. Approximately 21% of patients discontinued treatment because of adverse events. There is a risk of life-changing toxicity.
- Other ICI trials have not shown consistent results.
- Prospective biomarker analyses to predict outcomes and adverse events are not available.

Table 2 – Summary of recommendations from the European Association of Urology RCC Guidelines Panel on the use of adjuvant ICI and subsequent therapy for RCC

Recommendation	Strength rating
Offer adjuvant pembrolizumab to patients with clear-cell RCC, preferably within 12–16 wk after nephrectomy, with recurrence risk as defined in the KEYNOTE-564 trial: **Intermediate-high risk:** • pT2, grade 4 or sarcomatoid differentiation, 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 within 1 yr after nephrectomy	Strong
If adjuvant therapy is planned: • Discuss the contradictory results available from adjuvant ICI trials with the patient to facilitate shared decision-making • Inform the patient about the potential risk of overtreatment and immune-related side effects if adjuvant therapy is considered	Strong
Do not offer ICI monotherapy or combination therapy to patients with recurrence during or within 6 mo after adjuvant pembrolizumab	Weak

ICI = immune checkpoint inhibitor; NED = no evidence of disease; RCC = renal cell carcinoma.

The panel strongly feels that biomarker analyses should be performed in all of these trials to identify patients who will respond to therapy and give a better explanation for the inconsistent results. KIM-1 could be one potential biomarker, as retrospectively assessed in IMmotion010, because TNM-based risk eligibility criteria are not sufficient [10,11]. Treatment of unselected patients in the adjuvant setting on the basis of the KEYNOTE-564 criteria results unnecessary therapy in a proportion of patients. In the setting of the OS data available but signals of overtreatment and side effects and an absence of appropriate biomarkers, the patient preference should be the leading factor in shared decision-making.

3.2. *Treatment of patients with recurrence after adjuvant pembrolizumab*

There are currently no data available from prospective trials to guide treatment of patients with recurrence after adjuvant pembrolizumab. The panel defined different categories for patients with recurrence on or after pembrolizumab therapy:

- Early recurrence: patients with ICI-refractory disease with recurrence within the first 6 mo of adjuvant pembrolizumab.
- Intermediate recurrence: patients with recurrence later than 6 mo after starting and within the first 6 mo after finishing adjuvant pembrolizumab treatment.
- Late recurrence: patients with recurrence later than at least 6 mo after finishing adjuvant pembrolizumab treatment.

The CONTACT-03 and TiNivo2 randomised phase 3 trials in metastatic RCC showed no additional benefit of TKI + ICI combinations over single-agent TKI in patients who previously received ICI treatment. While CONTACT-03 and TiNivo-2 included patients with progression during previous ICI therapy in the metastatic setting, a recent retrospective analysis also suggested no benefit from ICI rechallenge after adjuvant pembrolizumab failure [12–14]. It is therefore likely that the groups with early or intermediate recurrence after adjuvant pembrolizumab may not benefit from a subsequent ICI therapy and should be treated with TKI monotherapy at systemic relapse. For patients with late recurrence, a benefit cannot be either excluded or confirmed. In this scenario, ICI rechallenge may be considered, especially for patients with a longer interval since finishing pembrolizumab.

4. Conclusions

The panel issues a strong recommendation for the use of adjuvant pembrolizumab therapy in patients with a higher risk of relapse and a weak recommendation not to treat patients with recurrence under or after initiating adjuvant pembrolizumab with a subsequent PD-1/PD-L1 ICI (Table 2).

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Study concept and design: Bedke, Bex.
Acquisition of data: Bedke, Bex.
Analysis and interpretation of data: Bedke, Bex.
Drafting of the manuscript: Bedke, Bex.
Critical revision of the manuscript for important intellectual content: Bedke, Abu Ghanem, Albiges, Bonn, Campi, Capitanio, Dabestani, Hora, Klatte, Kuusk, Lund, Marconi, Palumbo, Pignot, Powles, Tran, Volpe, Bex.
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Supplementary material

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