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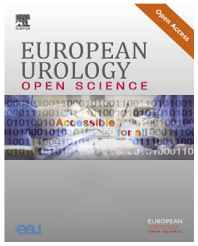

European Association of Urology

Research Letter: Open Science

Is Adjuvant Immunotherapy Worth for All Patients with Clear-cell Renal Cell Carcinoma at High Risk of Recurrence?

Results from the KEYNOTE-564 trial were published 1 yr ago in the *New England Journal of Medicine* [1]. Patients with clear-cell renal cell carcinoma (ccRCC) who met the protocol-defined criteria for high risk of recurrence (stage T2 with nuclear grade 4 or sarcomatoid differentiation, stage ≥T3, regional lymph-node metastasis, or stage M1 with no evidence of disease [NED]) were randomly assigned to receive either adjuvant pembrolizumab or placebo. The primary endpoint was disease-free survival (DFS). Within this pivotal randomized clinical trial, treatment with pembrolizumab showed a disease-free survival (DFS) benefit compared to placebo (DFS at 24 mo: 77.3% vs 68.1%) [1]. Grade ≥3 adverse events occurred in 32.4% of the patients who received pembrolizumab and 17.7% of those who received placebo. In the updated analysis after 30 mo of follow-up, adjuvant pembrolizumab continued to show a benefit in DFS compared with placebo (hazard ratio 0.63, 95% confidence interval 0.50–0.80) [2] both in the intention-to-treat population and across several prespecified and exploratory subgroups. Subgroup analyses showed a benefit irrespective of the presence of sarcomatoid features, nuclear tumor grade 4, or M1 with NED status at baseline, although the numbers in some subgroups were small and should be interpreted with caution [2]. The safety profile of adjuvant pembrolizumab remained consistent with the primary findings of the study [1]. However, overall survival (OS) data are still immature.

In this scenario, both the European Association of Urology and European Society of Medical Oncology changed their guidelines, introducing a (weak) recommendation for adjuvant pembrolizumab following surgery with curative intent in patients with ccRCC meeting the KEYNOTE-564 study criteria [3,4]. Accordingly, the European Medicines Agency approved the use of pembrolizumab as monotherapy in the adjuvant setting [5].

Notably, several issues regarding patient selection and the cost-effectiveness of adjuvant immunotherapy need to be addressed.

First, while patient selection is key, achieving this goal in clinical practice is still an unmet need. Namely, understanding how to pick the right patients from eligible candidates (for whom the risk of treatment-related harm may be worth the benefit) is complex and nuanced.

From an oncological standpoint, patients with non-metastatic ccRCC who might be offered adjuvant immunotherapy may harbor heterogeneous disease entities that cannot be captured by the KEYNOTE-564 criteria [1]. According to the Leibovich score [6] and the ECOG-ACRIN 2805 (ASSURE) prognostic model [7], the estimated 5-yr DFS varies significantly in each KEYNOTE-564 risk group (Table 1). While these models are not devoid of limitations [6,7], specific prognostic factors (eg, tumor size, World Health Organization/International Society of Urological Pathology grade, presence of necrosis, and vascular invasion, integrated into the above-mentioned scores) might play a key role in modulating the risk of recurrence in individual patients. Overall, the estimated 5-yr DFS among eligible patients may range from 12% to 95% according to the Leibovich score [6] and from 8% to 79% according to the ASSURE model [7]. Therefore, although DFS might not necessarily be a reliable surrogate metric for OS [8], we might argue that the higher the risk of recurrence, the better is the cost/benefit ratio for adjuvant pembrolizumab. Interestingly, in our prospectively collected multicenter data set (n = 681 consecutive patients with M0 ccRCC treated between 2015 and 2021 at Careggi Hospital, San Luigi Hospital, and UZ Leuven), 26% of the patients could have met the KEYNOTE-564 eligibility criteria, most of whom (87%) had pT3a N0 stage. While these patients would have been classified as at "intermediate-high" risk, their estimated 5-yr DFS could range significantly (Table 1), underlying the need to better stratify "eligible" patients using available prognostic models [3,4].

A second issue concerns the potential value of lymph node dissection (LND) in the new era of adjuvant immunotherapy. While patients with pN+ disease represent ideal candidates for adjuvant pembrolizumab [9] (with an estimated 5-yr DFS ranging from 8% to 56% according to the ASSURE model [7]; Table 1), in our data set only 6% of eligible patients had pN+ disease (of whom almost all had pT3–4 ccRCC). This finding highlights the current controversies regarding the anatomical templates and potential benefits of LND for RCC [10]. In fact, current guidelines recommend removal of "clinically enlarged lymph nodes for staging, prognosis and follow-up implications", and not to offer extended LND to patients with organ-confined disease [3]. However, in patients with cN0 locally advanced disease, pN status might be key in stratifying those at higher risk of relapse after surgery (Table 1) and could refine decision-making.

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Table 1 – Estimated 5 - yr MFS (according to the Leibovich score [6]) and 5 - yr DFS (according to the ASSURE model [7]) for all patients eligible for adjuvant immunotherapy according to the KEYNOTE - 564 study criteria [1], stratified by pT stage, pN stage , and W orld Health Organization /International Society of Urological Pathology grade.

Patients with ccRCC meeting the eligibility criteria for adjuvant pembrolizumab according to the KN-564 study [1]				Estimated 5-y MFS according to the Leibovich score [6]			Estimated 5-y DFS according to the ASSURE prognostic model [7]		
pT stage	**pN stage**	**Grade**	**KN-564 Risk Group** [1]	**Leibovich *Score*** (Range)	**Estimated 5-y MFS according to Leibovich *Score***	**Range of Leibovich *Risk Groups* (Estimated 5-y MFS)**	**DFS *Points*** [7] (Range)	**5-y estimated DFS according to DFS *Points*** *(online calculator)#*	**Range of *Risk Groups* (5-y estimated DFS)**
T1a	N+	Any	HIGH-RISK	2 to 6	40% to 95%	LOW to HIGH (31% to 97%)	7.5 to 11	25% to 56%	INT to HIGH (33% to 61%)
T1b	N+	Any		4 to 8	12% to 75%	INT to HIGH (31% to 74%)	7.5 to 11		
T2a	N0	G4	INT-HIGH RISK	6 to 7	32% to 40%	HIGH (31%)	8.0 to 9.5	37% to 52%	INT to HIGH (33% to 61%)
T2a	N+	Any	HIGH-RISK	5 to 9	12% to 63%	INT to HIGH (31% to 74%)	11 to 12.5	17% to 45%	HIGH (33%)
T2b	N0	G4	INT-HIGH RISK	7 to 8	12% to 32%	HIGH (31%)	9 to 10.5	29% to 43%	
T2b	N+	Any	HIGH-RISK	6 to 10	12% to 40%		12 to 13.5	12% to 37%	
T3a	N0	G1-G2	INT-HIGH RISK	4 to 6	40% to 75%	INT to HIGH (31% to 74%)	5.5 to 9.5	*without vascular invasion:* 46% to 79%; *WITH vascular invasion:* 37% to 72%	LOW to HIGH (33% to 83%)
T3a	N0	G3		5 to 7	31% to 63%		5.5 to 9.5		
T3a	N0	G4		7 to 9	12% to 31%	HIGH (31%)	7.5 to 11.5	*without vascular invasion:* 29% to 63% *WITH vascular invasion:* 22% to 55%	INT to HIGH (33% to 61%)
T3a	N+	G1-G2	HIGH-RISK	6 to 8	12% to 40%	HIGH (31%)	8.5 to 12.5	*without vascular invasion:* 23% to 56%; *WITH vascular invasion:* 17% to 48%	HIGH (33%)
T3a	N+	G3		7 to 9	12% to 31%		8.5 to 12.5		
T3a	N+	G4		9 to 11	12%		10.5 to 14.5	*without vascular invasion:* 12% to 38% *WITH vascular invasion:* 8.0% to 30%	
T3b	N0	G1-G2	INT-HIGH RISK	4 to 6	40% to 75%	INT to HIGH (31% to 74%)	5.5 to 9.5	38% to 72%	LOW to HIGH (33% to 83%)
T3b	N0	G3		5 to 7	31% to 63%		5.5 to 9.5		
T3b	N0	G4		7 to 9	12% to 31%	HIGH (31%)	7.5 to 11.5	22% to 54%	INT to HIGH (33% to 61%)
T3b	N+	G1-G2	HIGH-RISK	6 to 8	12% to 40%	HIGH (31%)	8.5 to 12.5	17% to 48%	HIGH (33%)
T3b	N+	G3		7 to 9	12% to 31%		8.5 to 12.5		
T3b	N+	G4		9 to 11	12%		10.5 to 14.5	8% to 18%	
T3c	N0	G1-G2	INT-HIGH RISK	4 to 6	40% to 75%	INT to HIGH (31% to 74%)	5.5 to 9.5	37% to 72%	LOW to HIGH (33% to 83%)
T3c	N0	G3		5 to 7	31% to 63%		5.5 to 9.5		
T3c	N0	G4		7 to 9	12% to 31%	HIGH (31%)	7.5 to 11.5	22% to 54%	INT to HIGH (33% to 61%)
T3c	N+	G1-G2	HIGH-RISK	6 to 8	12% to 40%	HIGH (31%)	8.5 to 12.5	17% to 48%	HIGH (33%)
T3c	N+	G3		7 to 9	12% to 31%		8.5 to 12.5		
T3c	N+	G4		9 to 11	12%		10.5 to 14.5	8% to 18%	
T4	N0	G1-G2	HIGH-RISK	4 to 6	40% to 75%	INT to HIGH (31% to 74%)	4.5 to 9.5	*without vascular invasion* 46% to 79%; *WITH vascular invasion:* 37% 72%	LOW to HIGH (33% to 83%)
T4	N0	G3		5 to 7	31% to 63%		4.5 to 9.5		
T4	N0	G4		7 to 9	12% to 31%	HIGH (31%)	6.5 to 11.5	*without vascular invasion* 29% to 63%; *WITH vascular invasion:* 22% to 54%	INT to HIGH (33% to 61%)
T4	N+	G1-G2	HIGH-RISK	6 to 8	12% to 40%	HIGH (31%)	7.5 to 12.5	*without vascular invasion* 23% to 56%; *WITH vascular invasion:* 17% to 48%	INT to HIGH (33% to 61%)
T4	N+	G3		7 to 9	12% to 31%		7.5 to 12.5		
T4	N+	G4		9 to 11	12%		9.5 to 14.5	*without vascular invasion* 12% to 38% *WITH vascular invasion:* 8% to 30%	HIGH (33%)

aPembro = adjuvant pembrolizumab; ccRCC = clear - cell renal cell carcinoma; DFS = disease - free survival; HiR = high risk; IR = intermediate risk; KN - 564 KEYNOTE - 564 study; LR = low risk; LS = Leibovich score; MFS = metastasis - free survival VI = va scular invasion .
a Using the online calculator at https://cancernomograms.com/nomograms/492.

Third, the differential impact of adjuvant immunotherapy on DFS and OS across patient populations (M0 vs M1 NED) is still a matter of debate [4]. In the KEYNOTE-564 trial, M1 NED status was defined as complete resection of all metastases at the time of or within 1 yr after nephrectomy [1]. Notably, patients with oligometastatic RCC represent a heterogeneous cohort that requires a multidisciplinary approach. In this context, the potential value of (cytoreductive) nephrectomy plus complete metastasectomy followed by adjuvant pembrolizumab versus upfront PD-1-based combination therapy requires further investigation [3,4].

Lastly, as a non-negligible proportion of patients with ccRCC could meet the KEYNOTE-564 eligibility criteria, the cost-effectiveness and economic sustainability of adjuvant immunotherapy must be carefully assessed, especially in single-payer health care systems.

A recent study using a decision analytic Markov model found that adjuvant pembrolizumab was not cost-effective at a 5-yr time horizon. In fact, at current prices, pembrolizumab was found to be cost-effective only for the subset of ccRCC patients highest risk 5 yr after treatment (including patients with complete metastasectomy, regional lymph node involvement, or pT3 tumors >7 cm with sarcomatoid features) [11].

Given the increasing costs of managing cancer as new agents become available [12] and the current lack of predictive biomarkers, further research is needed to refine patient selection for adjuvant immunotherapy, taking into consideration a variety of factors including granular tumor features (modulating the risk of recurrence; Table 1), the expected survival benefit, treatment-related toxicity, ands patients' life expectancy, quality of life, and preferences.

The applicability of the KEYNOTE-564 findings in real-life scenarios should also be investigated before recommending adjuvant pembrolizumab for all-comers [13].

In summary, despite the positive findings from the KEYNOTE-564 trial [1,2], several unmet clinical needs remain. Furthermore, results from other three adjuvant immune checkpoint inhibitor trials (IMmotion010 [14], PROSPER [15], and CheckMate-914 [16]) have recently been reported. Unfortunately, none of these trials met their primary endpoint (improvement in DFS in comparison to placebo or observation), calling again into question the benefits of adjuvant therapy in the field of RCC. Although the explanation for such contradictory results is complex and is likely to be multifactorial, further steps are needed to optimize patient selection (using clinical and molecular biomarkers) and improve the value proposition of adjuvant pembrolizumab for ccRCC at high risk of recurrence.

While we await robust OS data from the KEYNOTE-564 trial, as well as results from the multiarm, multistage RAMPART trial [17] and the LITESPARK-022 trial [18], individualized shared decision-making will be key to reducing the risk of overtreatment by selecting those patients who are most likely to benefit from adjuvant immunotherapy.

Conflicts of interest: The authors have nothing to disclose.

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