Kidney cancer

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Adjuvant personalized cancer vaccine: is this the end of metastatic kidney cancer

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The first study of personalized cancer vaccines for renal cell carcinoma with breakthrough results in the adjuvant setting has been published, showing a 100% efficacy rate and negligible toxic effects. However, important questions remain concerning long-term effectiveness.

Refers to Braun, D. A. et al. A neoantigen vaccine generates antitumour immunity in renal cell carcinoma. *Nature* https://doi.org/10.1038/s41586-024-08507-5 (2025).

Despite substantial advances in the treatment of metastatic renal cell carcinoma (mRCC), cure remains rare. Thus, preventing metastasis in patients diagnosed with localized RCC is the ultimate goal. Adjuvant treatment with the immune checkpoint inhibitor (ICI) pembrolizumab has been established in patients at risk of relapse; however, many patients still experience disease progression despite receiving adjuvant therapy. Additionally, treatment-related adverse events, particularly immune-related adverse events, are not negligible. Most of these events are reversible, but some can lead to lifelong changes, such as the development of insulin-dependent diabetes. Thus, the ideal adjuvant treatment should be effective in all patients and cause few or no toxic effects. A recent phase I study of personalized cancer vaccines (PCVs) by Braun et al.[1] suggests that such an ideal treatment could soon be within reach.

The introduction of ICIs in mRCC has been a breakthrough for advanced or metastatic kidney cancer. In 2021, the success of ICIs in mRCC was expanded to earlier stages of the disease, specifically the adjuvant setting of clear cell RCC (ccRCC), becoming the current standard of care. The PD1 ICI pembrolizumab has been shown to improve disease-free survival and overall survival (OS) in patients at high risk of relapse after surgery with curative intent[2,3]. When compared with patients in the placebo arm, more patients in the pembrolizumab arm were free of recurrence at 48 months' follow-up duration (56.6% versus 64.9%, HR 0.72, 95% CI 0.59–0.87). This result translated into a statistically significant improvement in OS, with an estimated 38% reduced risk of death for patients in the pembrolizumab arm compared with those in the placebo arm (HR 0.62, 95% CI 0.44–0.87, $P = 0.005$). Importantly, pembrolizumab is the first adjuvant RCC therapy to show an OS benefit. However, toxic effects in the pembrolizumab arm were not negligible. Adverse events of any grade and grade 3 or 4 occurred in 79.1% and 18.6% of patients, respectively, and required treatment discontinuation in 21.1%. These data must be viewed in the context that adjuvant treatments have a lower threshold for acceptable toxic effects than systemic treatments for advanced disease, as patients are considered healthy after surgery with curative intent. Pembrolizumab is an important advance in RCC management, but strategies with increased efficacy and reduced toxic effects are still needed in the adjuvant setting. Furthermore, other trials using ICIs in the adjuvant setting have failed[4–7] (Table 1), suggesting that more refined strategies are required to engage the immune system in eliminating micrometastases after surgery.

Individualized cancer therapy, including vaccination, has always been viewed as an elegant strategy. Autologous tumour cell vaccines have been investigated in RCC previously, but only one study[8] reported a disease-free survival benefit for the vaccine compared with observation (HR 1.58 after 5 years' follow-up duration). However, this trial had major limitations, including differences in attrition rates between groups, a lack of survival data, limited follow-up monitoring and heterogeneity in the patient population, which included patients with varying tumour stages and characteristics; therefore, the results were unreliable.

Now, two decades later, adjuvant vaccine strategies are evolving. PCVs show promise in ccRCC. In their preclinical and clinical work, Braun et al.[1] have successfully developed PCVs targeting neoantigens derived from tumour-specific mutations in tumours from nine patients with RCC after surgery. The authors reported that vaccination triggered T cell immune responses against PCV antigens in 100% of patients, including RCC driver mutations in *VHL*, *PBRM1*, *BAP1*, *KDM5C* and *PIK3CA*. Moreover, vaccination led to durable expansion of peripheral T cell clones as well as T cell reactivity against autologous tumours in seven out of nine patients. Remarkably, no patients experienced disease recurrence after a median follow-up duration of 40.2 months, and toxic effects were largely confined to grade 1, with minimal grade 2 occurrences. Based on the results of this phase I study, this neoantigen vaccine therapy could be viewed as a model for the ultimate ideal adjuvant treatment, as 100% of patients experienced the desired outcome – absence of disease recurrence and negligible toxic effects.

These phase I data represent a substantial step forward in the treatment of RCC. If this strategy holds its promise with longer follow-up duration and in large-scale trials, a dramatic reduction – or even elimination – of RCC recurrences after surgery might occur. For now, the results of this study raise several important questions that must be addressed to improve patient care in the adjuvant setting.

First, whether and/or which ICIs will be needed and when in the treatment course they should be given to optimize responses to PCVs needs to be discerned. In the study by Braun et al.[1], no major differences in immune response were observed between patients who received low-dose ipilimumab together with the vaccine and those who did not. However, larger studies are required to define the role of CTLA4 blockade in the context of neoantigen PCV therapy. Additionally, other combinations might be of interest, as the authors observed that PCV-induced circulating programmes could impair antitumour immunity, such as an increase in angiogenic factors or upregulation of PD1, in serial plasma samples[1].

Second, whether the right patients are being treated and whether patients who would benefit are being missed needs to be investigated.

Table 1 | Adjuvant immunotherapy trials in renal cell carcinoma

Trial	Median follow-up duration (months)	Agents	Timing	Treatment duration	*n*	Risk groups	Histology	Primary end point	Hazard ratio for DFS and/or OS
Keynote-564 (refs. 2,3)[a]	57.2	Pembrolizumab	Surgery within 12 weeks before randomization	1 year (17 cycles)	496 498	pT2, G4/sarcomatoid, N0 or pT3, G3–4, N0 or pT4, any grade, N0 or pT any, any grade, N1 or M1-NED	Clear cell	DFS	0.72 (95% CI 0.59–0.87) 0.62 (95% CI 0.44–0.87, *P* = 0.005)
IMmotion010 (ref. 4)	44.7	Atezolizumab Placebo	Within 12 weeks after surgery	1 year	390 388	pT2, G4 or pT3a, G3–4 or pT3b, any grade or pT any, any grade, N1 or M1-NED	Clear cell and/or sarcomatoid component	DFS	0.93 (95% CI 0.75–1.15), *P* = 0.50
CheckMate 914 part A[5]	37	Nivolumab + ipilimumab Placebo	Surgery 4–12 weeks before randomization	6 months	206 411	pT2, G4 or pT3a, G3–4 or pT3b, any grade or pT any, any grade, N1 or M1	Clear cell	DFS	0.92 (95% CI 0.71–1.19), *P* = 0.53
CheckMate 914 part B[6]	27	Nivolumab	Surgery 4–12 weeks before randomization	6 months	411	pT2, G4 or pT3a, G3–4 or pT3b, any grade or pT any, any grade, N1 or M1	Clear cell	DFS	0.80 (95% CI 0.58–1.12), *P* = 0.19
PROSPER[7]	30.4	Nivolumab + surgery vs surgery + surveillance	Within 12 weeks of surgery	9 months	404 415	>cT2aN0M0 or cT anyN1M0	Clear cell and non-clear cell	RFS	0.94 (95% CI 0.74–1.121), *P* = 0.32

DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival. [a]This trial is the only one with a positive result.

Our current understanding of risk stratification for relapse is still inadequate. Parameters such as tumour size and grading are well established in most recurrence scores, but they are insufficient to reliably predict individual relapse risk. Biomarkers, such as circulating DNA, kidney-injury molecule 1 (refs. 9,10) and others, might improve prediction of the need for neoantigen PCV therapy. This ability is particularly important, as manufacture of this therapy will not be widely available and will probably be expensive.

Third, whether the benefits of neoantigen PCVs in the adjuvant setting can be extended to metastatic disease needs examining. The data from Braun et al.[1] will probably raise hope among patients with mRCC. However, understanding that fighting micrometastases is biologically very different from fighting macrometastases (in which tumour burden, intra-tumour heterogeneity and differences in immune responses might impair the responsiveness to vaccine therapy) is important.

In conclusion, increased follow-up durations and studies with larger patient numbers are needed to understand the full effect of neoantigen PCV therapy in early RCC management. Nevertheless, the work by Braun et al.[1] is the first study with breakthrough results in the adjuvant setting, showing a 100% efficacy rate and negligible toxic effects.

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Competing interests

The authors declare no competing interests.