Adjuvant therapy for renal cell carcinoma

An update to the Canadian Kidney Cancer Forum consensus statement

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Cite as: Lalani AKA, Lavallee LT. Adjuvant therapy for renal cell carcinoma: An update to the Canadian Kidney Cancer Forum consensus statement. *Can Urol Assoc J* 2026;20(3):E113-6. http://dx.doi.org/10.5489/cuaj.9685

INTRODUCTION

In 2023, a panel of experts from the Canadian Kidney Cancer Forum (CKCF) released a consensus statement offering guidance on the use of adjuvant therapy after nephrectomy for patients with renal cell carcinoma (RCC). This statement was written after the initial reporting of the KEYNOTE-564 trial, which included disease-free survival (DFS) outcomes.[1,2] The consensus statement addressed risk stratification, eligibility for adjuvant immune checkpoint inhibitors (ICIs), patient counseling, followup protocols, and treatment options for patients experiencing recurrence after adjuvant immunotherapy.[1,2]

This document provides an update on key topics related to adjuvant therapy for RCC, including updated results from the KEYNOTE-564 trial, and results of a survey of Canadian RCC specialists examining the impact of the new data on clinical practice.[3]

Summary of the previous consensus

The 2023 CKCF consensus statement discussed the potential role of adjuvant pembrolizumab based on the DFS benefit reported in the first KEYNOTE-564 publication.[1,2] The panel noted that pembrolizumab should be considered as an adjuvant therapy option for patients with clear-cell RCC who met trial inclusion criteria for the intermediate-to-high, high, or M1 NED risk groups. Key considerations included counseling patients about recurrence risk, side effects of pembrolizumab, and timing of referral and therapy. The 2023 statement emphasized the need for ongoing followup of KEYNOTE-564 regarding overall survival (OS) outcomes and treatments received at recurrence in the placebo group, in addition to incorporating new data from trials in the adjuvant RCC space.

Basis for this update

The KEYNOTE-564 trial reported OS improvement with pembrolizumab compared to placebo at a median followup of 57.2 months.[3,4] The hazard ratio (HR) for death was 0.62 (95% confidence interval [CI] 0.44–0.87, p=0.005), and the HR for DFS was 0.72 (95% CI 0.59–0.87) in favor of pembrolizumab. At 48 months, 91.2% of participants were alive in the pembrolizumab group compared to 86.0% in the placebo group (Table 1). Estimated DFS rates at 48 months were 64.9% with pembrolizumab and 56.6% with placebo.[3]

Pembrolizumab was associated with a higher incidence of serious adverse events (AEs) — 20.7% with pembrolizumab compared to 11.5% with placebo — and of grade 3 or 4 AEs — 18.6% with pembrolizumab compared to 1.2% with placebo. Immune-mediated AEs (IRAEs) and infusion reactions occurred in 36.5% of patients receiving pembrolizumab and 7.3% of those receiving placebo. IRAEs grade 3 or 4 occurred in 9.4% of patients receiving pembrolizumab and in 0.6% of those receiving placebo.[3]

When considering adjuvant therapy, it is important to note that all patients are exposed to these potential AEs, even those not destined to recur.

METHODS

To address updated reports from the KEYNOTE-564 clinical trial, we conducted a survey to determine physicians' perceptions of adjuvant therapy for RCC and any potential changes.[3] A JotForm online survey was conducted via the survey platform and via direct email outreach to physicians across Canada on July 17, 2025. Survey questions examined how updated data have influenced physicians' confidence in the trial design and results, clinical decision-making, referral patterns, and perceived patient acceptance of adjuvant pembrolizumab. Physician demographic information, including specialty, practice location, and years in practice were collected. Descriptive statistics were performed using Excel's data analysis tools.

RESULTS

Twenty-nine RCC experts in Canada were contacted to complete the survey and the response rate was 100%.

Respondent demographics

Respondents were primarily from Ontario (n=15, 52%), Quebec (n=7, 24%), and Alberta (n=4, 14%), with one respondent each from Manitoba, Nova Scotia, and British Columbia. Medical oncologists (48%) and urologists (48%) were equally represented, with one radiation oncologist participating. Slightly more than half (52%) had ≥10 years of clinical experience.

Confidence in trial design and results

Confidence in the KEYNOTE-564 trial design and results remained stable or increased (Figure 1). Respondents reporting no change emphasized that the trial was generally viewed as robust from the outset. Confidence in study results was reinforced with the reporting of OS benefit. Concerns regarding study design were consistent and centered around optimal patient selection specifically related to inclusion of M1 NED and pT2G4 populations, the need for improved risk-stratification tools, and differential access to immunotherapy after recurrence and its potential impact on OS interpretation.

Likelihood of recommending adjuvant therapy

There was increased willingness to recommend adjuvant pembrolizumab among some respondents (45%), while others reported no change (45%) (Figure 1). Those more inclined to recommend therapy cited greater confidence in discussing survival benefit and access to tools to support informed patient decision-making. Respondents expressing restraint emphasized ongoing uncertainty regarding the benefit magnitude in specific subgroups, particularly M1 NED and intermediate-risk patients. There were some concerns about overtreatment and uncertainty about KEYNOTE-564 generalizability to health systems with good access to immunotherapy at recurrence.[5-8]

Table 1. Overall survival, disease-free survival, and adverse events in the intention-to-treat (ITT) population of the KEYNOTE-564 study[2,3]

Intention to treat population	Overall survival	Disease-free survival	Any-grade adverse event	Serious adverse event
Absolute risk reduction with pembrolizumab (48 months)	5.2%	8.3%	–	
Hazard ratio (95% CI; 57.2 months)	0.62 (0.44–0.87)	0.72 (0.59–0.87)		
Absolute risk increase with pembrolizumab	–	–	26.1%	9.2%

CI: confidence interval.

Impact on referral patterns

Most clinicians (55%) reported stable or increased referrals to discuss adjuvant pembrolizumab (Figure 1). Increases were most often reported by urologists (50%) and early-career physicians, and were attributed to the reported OS benefit, increased awareness, and expanding reimbursement.

Patient acceptance

Physicians generally perceived patient acceptance of adjuvant therapy as stable, with modest increases attributed to OS benefit (Figure 1). Several respondents noted variability in patient understanding of absolute benefit and risk-benefit tradeoffs.

DISCUSSION

Access to effective adjuvant therapy is of interest to patients with an increased risk of recurrence after surgery. In this report we examined trial data reported since the 2023 CKCF consensus statement on adjuvant therapy for RCC and completed a survey capturing Canadian RCC experts' perspectives. Overall, survey responses reflect measured integration of adjuvant pembrolizumab rather than wholesale change.

OS benefit was the primary driver of confidence and clinical uptake. Optimal patient selection, unanswered questions regarding treatment at recurrence in KEYNOTE-564, and the need for accurate predictive tools remain key concerns.

Approximately half of respondents reported being more likely to recommend adjuvant pembrolizumab, citing improved confidence in survival outcomes and improved comfort with patient counseling. Many clinicians reported no change in practice and highlighted that adjuvant pembrolizumab provided modest absolute survival gains and significantly higher toxicity, echoing themes from recent international guidance emphasizing individualized risk assessment and shared decision-making.[9-11]

Referral patterns and perceived patient acceptance both suggest increased openness to adjuvant therapy, with a desire for educational tools to contextualize benefit, uncertainty, and risk. Concerns also remain regarding how the use of adjuvant single-agent pembrolizumab may impact treatment options for patients who recur during or within six months of adjuvant therapy.

Limitations

This study has several limitations and should be interpreted in the context of the design. The survey sample size was small (n=29), which may limit the generalizability of findings. Geographic representation was also

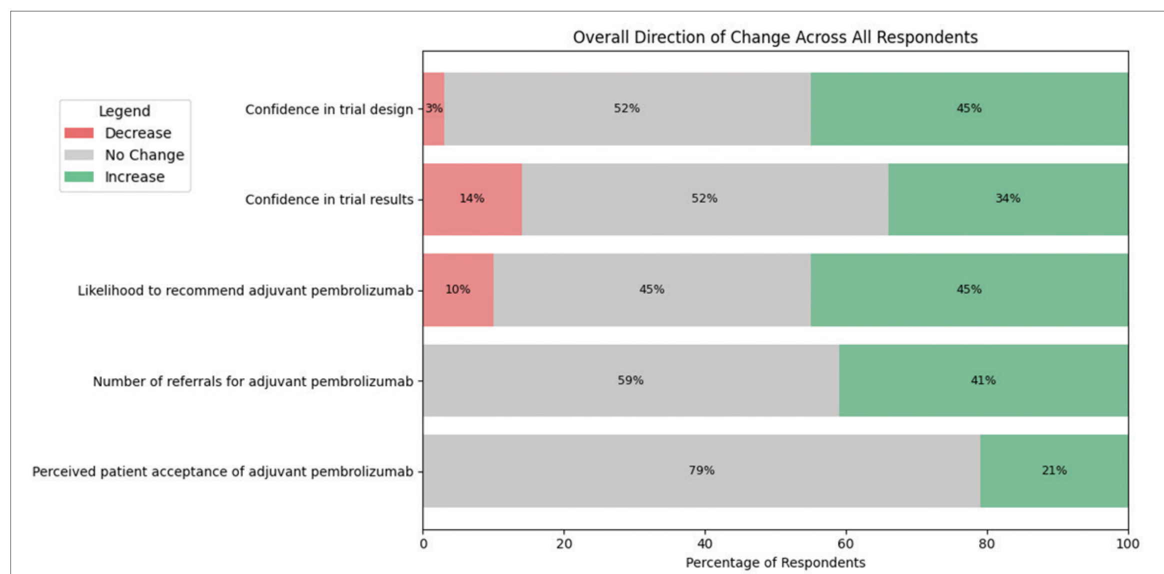

Figure 1. Overall direction of change across all respondents. Diverging bar chart summarizing the proportion of respondents reporting less (red bar), no change (grey bar), or more across five domains related to use of adjuvant pembrolizumab for ccRCC. Percentages within each segment indicate the share of respondents selecting that option (n=29).

constrained, with the majority of respondents practicing in Ontario and Quebec; however, the response rate was 100%, therefore, these may represent the providers who are highly invested in RCC care and research nationally.

FUTURE DIRECTION

Survey responses reflect perceptions of the adjuvant RCC landscape informed by the latest published KEYNOTE-564 report. Recently, further data readouts of KEYNOTE-564 and other studies in the adjuvant RCC space have occurred.

At ASCO 2025, Haas et al presented results from the fourth prespecified interim analysis of KEYNOTE-564 with a minimum followup of five years (median 69.5 months). Point estimates for DFS (HR 0.71, 95% CI 0.59–0.86) and OS (HR 0.66, 95% CI 0.48–0.90) were consistent with prior analyses. At the time of this writing, these data have not yet been published in a peer-reviewed journal.[12]

At the 2025 ESMO congress, initial results of the three-arm RAMPART trial were presented.[13] Specifically, data from the combination durvalumab and tremelimumab arm (n=225) were compared to the active monitoring arm (n=340) and showed that three-year DFS was 81% vs 73%, respectively. Prespecified, prepowered subgroup analyses further revealed that this benefit was restricted to the high-risk population (Leibovich score 6–11) with HR 0.52, compared to the intermediate-risk population (Leibovich score 3–5) with HR 1.19. Further data from the durvalumab monotherapy arm, as well as an OS readout, are anticipated to help contextualize the risk-benefit profile of dual checkpoint blockade in this clinical setting.

Furthermore, in a press release dated October 2025, industry announcements indicated that the Litespark-022 clinical trial was positive for the primary endpoint of DFS.[14] This trial (n=1841) evaluated pembrolizumab with belzutifan vs. pembrolizumab with placebo in patients with resected RCC. Precise data readouts, including the secondary endpoint of OS, are needed to assess implications for clinical practice.

Future publication of these trials will provide important information that may impact the management of patients with RCC at high risk of recurrence after surgery; however, at the time of this writing, neither study has been published and thus does not impact clinical care. Given the evolving literature in this setting, the Canadian Urological Association is planning a guideline on adjuvant therapy for patients with RCC using rigorous GRADE methodology to help synthesize the data and better inform physicians.

COMPETING INTERESTS: Dr. Lalani has received compensation from Astellas, AstraZeneca, Bayer, BMS, Eisai, Ipsen, J&J, Merck, Novartis, Pfizer, and Tersera, and honoraria from BioCanRx. Dr. Lavallée has participated in advisory boards (unrelated) for Abbvie, Astellas, Bayer Ferring, Knight, Merck, and Tolmar.

ACKNOWLEDGMENTS: The authors thank Anna Vainshtein, PhD (Craft Science Inc.), for medical writing and editorial support in the development of this manuscript, and Sharlini Yogasingam (Canadian Urological Association) for assistance with survey administration and analysis.

This paper has been peer-reviewed.

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