

## Adjuvant therapy for renal cell carcinoma: 2023 Canadian Kidney Cancer Forum consensus statement

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### ABSTRACT

**INTRODUCTION:** Several recent randomized trials evaluated the impact of adjuvant immune checkpoint inhibitor (ICI)-based therapy on post-surgical outcomes in renal cell carcinoma (RCC), with disparate results. The objective of this consensus statement is to provide data-driven guidance regarding the use of ICIs after complete resection of clear-cell RCC in a Canadian context.

**METHODS:** An expert panel of genitourinary medical oncologists, urologic oncologists, and radiation oncologists with expertise in RCC management was convened in a dedicated session during the 2022 Canadian Kidney Cancer Forum in Toronto, Canada. Topic statements on the management of patients after surgery for RCC, including counselling, risk stratification, indications for medical oncology referral, appropriate followup, eligibility and management for adjuvant ICIs, as well as treatment options for patients with recurrence who received

adjuvant immunotherapy, were discussed. Participants were asked to vote if they agreed or disagreed with each statement. *Consensus* was achieved if greater than 75% of participants agreed with the topic statement.

**RESULTS:** A total of 22 RCC experts voted on 14 statements. Consensus was achieved on all topic statements. The panel felt patients with clear-cell RCC at increased risk of recurrence after surgery, as per the Keynote-564 group definitions, should be counselled about recurrence risk by a urologist, should be informed about the potential role of adjuvant ICI systemic therapy, and be offered referral to discuss risks and benefits with a medical oncologist. The panel felt that one year of pembrolizumab is currently the only regimen that should be considered if adjuvant therapy is selected. Panelists emphasized current opinions are based on disease-free survival given the available results. Significant uncertainty regarding the benefit and harms of adjuvant therapy remains, primarily due to a lack of consistent benefit observed across similar trials of adjuvant ICI-based therapies and immature overall survival (OS) data.

**CONCLUSIONS:** This consensus document provides guidance from Canadian RCC experts regarding the potential role of ICI-based adjuvant systemic therapy after surgery. This rapidly evolving field requires frequent evidence-based re-evaluation.

### INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal malignancy. At the time of diagnosis, approximately 65% of patients have non-metastatic disease, while the remainder are metastatic.<sup>1</sup> The standard of care for patients with non-metastatic tumors is surgical resection with radical or partial nephrectomy. Some patients with small tumors may also be eligible for ablative therapies, radiotherapy, or active surveillance.<sup>2</sup> Currently, patients who undergo surgery for clinically localized tumors are monitored using history, physical

examination, and laboratory and imaging tests aimed at the early detection of local or metastatic tumor recurrence, new renal primary tumors, postoperative complications, and renal impairment.

The risk of recurrence after nephrectomy varies by tumor-specific and clinical factors, including tumor stage, grade, and histological subtype (clear-cell, papillary, chromophobe, etc.).<sup>3-6</sup> Tumor stage is the most important prognostic variable. Numerous nomograms are available to estimate the risk of recurrence, although the accuracy of these nomograms and consensus regarding the optimal model are lacking.<sup>7-11</sup> The estimated risk of recurrence can be used to personalize the followup schedule to ensure that patients with a greater risk receive timely and more frequent investigations, while those at low risk are spared the inconvenience, risks, and cost of intensive followup.<sup>12</sup>

For years, investigators have attempted to develop adjuvant therapies benefiting patients at increased risk of cancer recurrence after partial or radical nephrectomy.<sup>13</sup> Adjuvant therapy should aim to reduce the risk of cancer recurrence, improve overall survival (OS), and have an acceptable safety profile. Thus far, targeted therapies used in the metastatic RCC setting have not demonstrated meaningful benefits in the adjuvant setting.<sup>14-19</sup> More recently, multiple adjuvant trials leveraging immune checkpoint inhibitors (ICIs) have reported disparate clinical results.<sup>20-22</sup>

The objective of this consensus statement is to provide Canadian healthcare professionals guidance regarding the possible use of adjuvant therapies after surgery for RCC based on the best available evidence.

## METHODS

An expert panel of genitourinary medical, urologic, and radiation oncologists who are involved in RCC management and research was convened in a dedicated session during the 2022 Canadian Kidney Cancer Forum in Toronto, Canada (October 13–15, 2022). The purpose of the meeting was to discuss clinical trial data pertaining to adjuvant therapy for RCC and generate a consensus document to assist Canadian healthcare professionals and patients regarding best practices based on available data. Prior to the meeting, draft topic statements were generated by two authors, including one medical oncologist and one urologic oncologist (AKL and LL). A third author (AK) reviewed the topic statements prior to the meeting for clarity and completeness. Topic statements covered the management of patients after surgery for RCC, including counselling expectations after surgery, risk stratification, indications for medical oncology referral, appropriate followup investigations and timing, eligibility of patients for adjuvant therapies

based on disease characteristics, management during adjuvant therapy, and treatment options for patients with recurrence who received adjuvant therapy. A complete list of the topic statements is presented in Table 1.

During the session, meeting objectives were shared, each topic statement was presented, and relevant clinical trial data and evidence related to the topic statement were reviewed. Time was provided for open discussion and debate on each topic statement, and statements were modified in real-time to improve clarity and purpose. After each discussion, participants were asked to vote: agree or disagree with the topic statement. **Consensus** was achieved if greater than 75% of participants agreed with the topic statement. Statements for which 50–74% of participants agreed had **near consensus**, and statements with <50% agreement were considered to have **no consensus**.

Twenty-two healthcare professionals from five Canadian provinces participated in the consensus meeting, including eight urologic oncologists, 11 medical oncologists, and three radiation oncologists. Following that meeting, an initial draft was circulated, and email communication and discussions occurred to take into account updates; a final draft was reviewed and agreed upon by all authors.

## SUMMARY OF EVIDENCE

Adjuvant cancer therapy after surgery should target residual microscopic disease with curative intent. In appropriately selected patients, adjuvant therapy should reduce the risk of recurrence while exposing patients to a limited risk of morbidity. In RCC, targeted therapies, such as vascular endothelial growth factor tyrosine kinase inhibitors (VEGF-TKIs) or mechanistic target of rapamycin (mTOR) inhibitors, that are beneficial in the metastatic setting have not been found to improve survival or have acceptable tolerability in the adjuvant setting.<sup>14,17,19,23-26</sup> Sunitinib was shown in the S-TRAC trial to improve disease-free survival (DFS, by central review) but not OS, and had an unacceptable toxicity profile for the adjuvant setting.<sup>14,24</sup> While sunitinib was approved, based on the DFS data, by the U.S. Food and Drug Administration (FDA) and Canadian Agency for Drugs and Technologies in Health (CADTH), uptake in the real world has been limited.<sup>23</sup> Other systemic therapies, including cytokines, such as interferon alpha and interleukin-2 (IFN $\alpha$  and IL-2), and vaccines, have failed to demonstrate benefit in the adjuvant setting.<sup>27,28</sup> Therefore, effective adjuvant therapy for RCC has remained an area of unmet need.

Recently, various ICIs have been evaluated as adjuvant RCC therapy in large, randomized trials.

**Table 1. Consensus topic statements and results as voted at the CKCF meeting on October 15, 2022**

Statement	Consensus
1. Patients who have had surgery for RCC should be counseled by urologists on their risk of recurrence using validated prediction tools.	Achieved: 22 yes, 0 no (100%)
2. Patients should have fully resected clear cell RCC disease (localized or M1 NED) to be considered for adjuvant therapy.	Achieved: 20 yes, 1 no (95%)
3. Patients with resected clear cell RCC at elevated risk of recurrence should be informed about the potential role of adjuvant therapy and be offered a referral to medical oncology.	Achieved: 22 yes, 0 no (100%)
4. Patients should have staging including cross-sectional imaging of the chest/abdomen/pelvis prior to starting adjuvant therapy.	Achieved: 21 yes, 1 no (95%)
5. If adjuvant therapy is provided, it should be initiated within 12–16 weeks of surgery.	Achieved: 19 yes, 0 no (100%)
6. If adjuvant therapy is provided, pembrolizumab is currently the only treatment that should be considered.	Achieved: 18 yes, 0 no (100%)
7–9. Patients should be considered for adjuvant therapy based on the group definitions of Keynote-564.	
7. Patients with pT2 clear cell RCC grade 4 or with sarcomatoid features, and pT3 clear-cell RCC disease may be considered for adjuvant systemic therapy.	Achieved: 18 yes, 1 no (95%)
8. Patients with pT4 clear cell RCC of any grade and those with M1 clear cell RCC may be considered for adjuvant systemic therapy.	Achieved: 19 yes, 0 no (100%)
9. Patients with resected M1 clear-cell RCC and no evidence of disease (NED) may be considered for adjuvant systemic therapy.	Achieved: 16 yes, 1 no (94%)
10. If patients receive adjuvant pembrolizumab, the duration of treatment should be one year.	Achieved: 17 yes, 1 no (94%)
11. If patients receive adjuvant therapy, followup imaging should be performed every 3–6 months during therapy.	Achieved: 19 yes, 0 no (100%)
12. On completion of adjuvant therapy, followup surveillance should continue per guidelines for localized disease.	Achieved: 19 yes, 0 no (100%)
13. Patients who experience disease recurrence six months or more after completion of adjuvant therapy should be offered standard-of-care first-line treatment for metastatic disease.	Achieved: 19 yes, 0 no (100%)
14. Patients who experience disease recurrence during adjuvant therapy or within six months of completion should be treated similarly to patients who have progressed on first-line immunotherapy for metastatic disease.	Achieved: 20 yes, 0 no (100%)
RCC: renal cell carcinoma.	

Pembrolizumab, an anti-PD-1 antibody, was the first ICI to demonstrate a DFS benefit in the KEYNOTE-564 trial.<sup>20,29</sup> In this trial, patients with clear-cell RCC post-nephrectomy were randomized to one year of pembrolizumab every three weeks for up to one year or placebo. Patients were categorized based on their risk of cancer recurrence into three groups: intermediate-to-high-risk (pT2 with grade 4 or sarcomatoid features, or pT3), high-risk (pT4 or pTanyN1), or M1 NED (resected synchronous or metachronous metastases within 12 months of the initial nephrectomy with no evidence of residual disease) (Table 2). At 30 months

followup, treatment with pembrolizumab was associated with a 37% decrease in the risk of disease recurrence or death compared to placebo (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.50–0.80). The estimated DFS rate at 30 months was 75.2% vs. 65.5% in the pembrolizumab and placebo arms, respectively.

Preplanned exploratory subgroup analyses showed the greatest DFS benefit in M1 NED patients (HR 0.28, 95% CI 0.12–0.66), although these represented a minority of patients in the trial (n=29 per arm). It is premature to draw conclusions regarding OS differences for Keynote-564 at this time due to the limited number of events reached in the trial (death events n=46) and noting the protocol-defined timing of event-driven analyses for OS is pending. In this context, preliminary data slightly favors pembrolizumab compared to placebo, with an estimated 30-month OS of 95.7% vs. 91.4% (HR 0.52, 95% CI 0.31–0.86).

Of note, subsequent therapies provided to patients in both arms will have implications on interpreting OS data as it matures (see Discussion). Based on available data from Keynote-564, pembrolizumab was approved for use in the adjuvant setting by the U.S. FDA in November 2021,<sup>30</sup> the European Medicines Agency in January 2022, Health Canada in September 2022, and was recommended for reimbursement by CADTH<sup>31</sup> in October 2022.

It is important to interpret Keynote-564 in the context of other randomized trials investigating single-agent or combination immunotherapies in the adjuvant setting for RCC, which have not demonstrated benefit (Table 3). The IMmotion 010 trial randomized patients with resected intermediate-to-high-risk RCC (clear-cell and/or sarcomatoid component) to atezolizumab or placebo for one year.<sup>21</sup> Included patients had pT2 grade 4, pT3a grade 3 or 4, pT3b/c or pT4 or pN1 any grade, and patients with M1 NED (defined as synchronous metastasectomy or metachronous metastasectomy  $\geq 12$  months after primary surgery). At a median followup of 44.7 months, atezolizumab did not improve DFS compared to placebo (primary outcome): 24-month DFS was 67% for atezolizumab and 65% for placebo (median DFS 57.2 vs 49.5 months, HR 0.93, p=0.49). With 14% of OS events, median OS was not significantly different (HR 0.97, 95% CI 0.67–1.42).

The CheckMate 914 trial (Part A) randomized patients with resected clear-cell RCC (including sarcomatoid features) to 24 weeks of nivolumab (q2w  $\times$  12 doses) plus ipilimumab (q6w  $\times$  4 doses) or placebo.<sup>22</sup> This trial allowed patients with pT2a grade 3 or 4, or pT2b-pT4, or pN1 any grade. Of note, there was no M1 NED population included. At median followup of 37 months, the combination of nivolumab plus ipili-



**Table 2. Patients eligible for adjuvant pembrolizumab according to Keynote 064 definitions<sup>20</sup>**

Risk category	Characteristics
Intermediate-to-high-risk	pT2 with grade 4 or sarcomatoid features, or pT3
High-risk	pT4 or pTanyN1
M1 NED	Resected synchronous or metachronous metastases within 12 months of the initial nephrectomy with no evidence of residual disease

mumab did not improve DFS compared to placebo (primary outcome): 24-month DFS was 76.4% for the combination and 74% for placebo (median DFS NR vs. 50.7 months, HR 0.92,  $p=0.53$ ).

Finally, the PROSPER-RCC trial used a radiological entry point to randomize patients with localized RCC to preoperative nivolumab (one dose) followed by nephrectomy followed by postoperative nivolumab (nine doses) vs. immediate surgery followed by observation.<sup>32</sup> This trial allowed both clear-cell or non-clear-cell patients with  $\geq$ pT2, any N, M0 or oligometastatic M1 planned for definitive resection. Of note, the protocol was amended to require a biopsy only in patients randomized to the interventional (nivolumab) arm. At interim analysis, with median followup of 16 months, the Data and Safety Monitoring Committee (DSMC) stopped the trial for futility and relapse-free survival (RFS) was not different between the two arms (HR 0.95).

In the context of all available prospective, randomized data at the time of this meeting, we sought to provide guidance to clinicians and patients using the topic statements included below.

## STATEMENTS

### ■ STATEMENT 1

**Patients who have had surgery for RCC should be counselled by urologists on their risk of recurrence using validated prediction tools (consensus achieved: 100%).**

The risk of cancer recurrence varies after surgery based on several factors, including most notably tumor stage, tumor grade, histological subtype, and other clinicopathological variables.<sup>3-6</sup> Several nomograms have been created to calculate the risk of recurrence after surgery.<sup>7-11</sup> Urologists should discuss the surgical pathology and inform patients about their estimated risk of recurrence using available nomograms, while noting that nomograms may not entirely capture this risk. These estimates can guide clinical followup, such as the intensity

**Table 3. Summary of randomized placebo-controlled trials evaluating adjuvant therapy for renal cell carcinoma**

Trial	Agents (n) <sup>^</sup>	Disease-free survival HR (95% CI, p)	Overall survival HR (95% CI, p)
<b>Targeted therapies</b>			
S-TRAC <sup>14</sup>	Sunitinib (309)	0.76 (0.59–0.98, $p=0.003$ )	0.93 (0.67–1.29, $p=0.66$ )
	Placebo (306)		
ASSURE <sup>15,25</sup>	Sunitinib (647)	1.02 (0.85–1.23*, $p=0.8$ )	1.06 (0.78–1.45, $p=0.66$ )
	Placebo (647)		
SORCE <sup>16</sup>	Sorafenib (649)	0.97 (0.80–1.17*, $p=0.72$ )	0.80 (0.58–1.11, $p=0.12$ )
	Sorafenib 1 year (642)	0.94 (0.77–1.14, $p=0.51$ )	0.92 (0.71–1.20, $p=0.541$ )
	Placebo (430)		
SORCE <sup>16</sup>	Sorafenib 3 years (639)	1.01 (0.82–1.23, $p=0.95$ )	1.06 (0.82–1.38, $p=0.64$ )
	Placebo (430)		
EVEREST <sup>17</sup>	Everolimus (775)	0.85 (0.72–1.00, $p=0.025$ ) (RFS)	0.90 (0.71–1.13, $p=0.18$ )
PROTECT <sup>18</sup>	Pazopanib (769)	0.80 (0.68–0.95, $p=0.013$ )	0.82 (0.63–1.08, $p=0.16$ )
ATLAS <sup>19</sup>	Axitinib (363)	0.87 (0.66–1.15, $p=0.32$ )	1.03 (0.6–1.76, $p=0.92$ )
ATLAS <sup>19</sup>	Placebo (361)		
<b>Immune checkpoint inhibitors</b>			
Keynote-564 <sup>29</sup>	Pembrolizumab (496)	0.63 (0.50–0.80, $p<0.0001$ )	0.52 (0.31–0.86, $p=0.0048$ )**
Keynote-564 <sup>29</sup>	Placebo (498)		
Immotion010 <sup>21</sup>	Atezolizumab (390)	0.93 (0.75–1.17, $p=0.53$ )	0.97 (0.67–1.42)
Immotion010 <sup>21</sup>	Placebo (388)		
Checkmate 914 <sup>22</sup>	Nivolumab + Ipilimumab 6 months (405)	0.92 (0.71–1.19, $p=0.53$ )	NM
Checkmate 914 <sup>22</sup>	Placebo (411)		
PROSPER RCC <sup>32</sup>	Nivolumab [neo/adjuvant] (404)	0.97 (0.74–1.28, $p=0.43$ )	NM
PROSPER RCC <sup>32</sup>	Observation (415)		

<sup>^</sup>Duration of therapies for trials was 1 year unless otherwise indicated. \*97.5% CI. \*\*Limited followup, final overall survival analysis pending. CI: confidence interval; HR: hazard ratio; NM: not mature; RFS: recurrence-free survival.

and type of imaging performed, and inform decisions about the potential roles of adjuvant therapies.<sup>12</sup>

### ■ STATEMENT 2

**Patients should have fully resected clear-cell RCC disease (localized, N+M0, or M1 NED) to be considered for adjuvant therapy (consensus achieved: 95%).**

Adjuvant therapy refers to therapy aimed at reducing the risk of cancer recurrence. In clinical practice and trials, adjuvant therapies are offered to patients with fully resected disease that was either clinically localized or oligometastatic and fully resected (M1 NED) with negative surgical margins. Patients with unresected sites of malignancy should be considered for additional local treatments — where suitable and feasible — prior to

considering systemic treatment. If disease biology or clinical trajectory precludes complete local treatment, systemic therapy in the unresectable/metastatic setting could be considered.

#### ■ STATEMENT 3

**Patients with resected clear-cell RCC at elevated risk of recurrence should be informed about the potential role of adjuvant therapy and be offered a referral to medical oncology (consensus achieved: 100%).**

A discussion about surgical pathology and the risk of recurrence allows the urologist to introduce the role adjuvant therapy may serve for their patients. The possibility of adjuvant therapy as part of the care plan should be mentioned prior to surgery. Postoperatively, patients deemed at an elevated risk of recurrence, as defined by the Keynote-564 clinical trial<sup>20</sup> (Table 2), should be offered a referral to a medical oncologist to further discuss the risks and benefits of adjuvant systemic therapy. It should be noted that Keynote-564 required patients to have a clear-cell component on pathology. Therefore, data may not be applicable to non-clear-cell RCC histologies. Furthermore, the magnitude of benefit may vary based on the risk of cancer recurrence and each patient's medical history and competing risks.

#### ■ STATEMENT 4

**Patients should have staging, including cross-sectional imaging of the chest/abdomen/pelvis, prior to starting adjuvant therapy (consensus achieved: 95%).**

Patients should have staging imaging, including cross-sectional imaging of the chest, abdomen, and pelvis at a reasonable time course before initiating adjuvant therapy. While a specific timeline may vary by clinical or patient context, the panel felt a window of 6–12 weeks prior to start of adjuvant therapy is usually appropriate. Some patients may benefit from additional imaging, including brain imaging and bone scan, particularly with the presence of symptoms suggesting possible metastasis.

#### ■ STATEMENT 5

**If adjuvant therapy is provided, it should be initiated within 12–16 weeks of surgery (consensus achieved: 100%).**

Keynote-564 required patients to initiate adjuvant therapy within 12 weeks of surgery. The panel discussed this timeline on a patient and upstream level within the Canadian healthcare system. The panel believes that initiating adjuvant therapy within 12–16 weeks of surgery is reasonable in the real-world setting; however, at this

time, drug access in Canada necessitates commencement within 12 weeks of surgery.

#### ■ STATEMENT 6

**If adjuvant therapy is provided, pembrolizumab is currently the only treatment that should be considered (consensus achieved: 100%).**

The only ICI-based therapy that has demonstrated improvement in DFS as a primary endpoint is pembrolizumab in Keynote-564. The panel believes pembrolizumab should be the only agent considered in the adjuvant setting at the time of this writing.

While in other clinical treatment settings, PD-1/PD-L1 agents may be considered to have similar therapeutic activity, the panel did not feel that single-agent ICIs could be considered interchangeable in the adjuvant RCC setting unless other randomized data provides support to do so. Further, while combination ICIs have been approved in the advanced RCC setting,<sup>33,34</sup> in light of the negative CheckMate 914 study (which evaluated combination nivolumab and ipilimumab as adjuvant therapy), the panel felt combination ICIs should not be offered as an adjuvant option at this time, outside of clinical trials.

#### ■ STATEMENTS 7-9

**Patients should be considered for adjuvant therapy based on the group definitions of Keynote-564.**

The panel recommends that risk group definitions from the Keynote-564 trial be used for patient selection and counselling when considering adjuvant therapy (see statements 7–9 for definitions). Subgroup-specific information is important to consider because the risk of side effects (harm) from adjuvant therapy may be similar for all groups, while the benefit may not be equivalent. Subgroup-specific HRs from Keynote-564 have been provided below to help estimate the number needed to treat (NNT) to prevent one cancer recurrence or death. It should be noted that Keynote-564 was not powered to detect differences in specific subgroups, therefore, the HRs for each group should be interpreted with caution.

#### ■ STATEMENT 7

**Patients with pT2 clear-cell RCC grade 4 or with sarcomatoid features, and pT3 clear-cell RCC disease may be considered for adjuvant systemic therapy (consensus achieved: 95%).**

Patients with pT2 grade 4 clear-cell RCC or with sarcomatoid features, and pT3 clear-cell RCC disease

(Keynote-564 intermediate-high-risk group) may be offered adjuvant systemic therapy with pembrolizumab. Patients in this group randomized to receive one year of pembrolizumab (n=422) had improved DFS compared to placebo (n=433) after 30 months of followup: 81% vs. 72%, respectively (HR 0.68, 95% CI 0.52–0.89). This absolute risk reduction of 9% translates to 11 patients requiring a year of treatment with pembrolizumab to prevent one cancer recurrence at 30 months (NNT=11).

While not voted separately during this meeting, the authors considered the prognostic and potentially predictive value of sarcomatoid features in RCC. In Keynote-564 overall, 111 patients were classified as having sarcomatoid features present. Within this population, patients randomized to pembrolizumab had improved DFS compared to placebo after 30 months of followup: 71.8% vs. 52%, respectively (HR 0.54, 95% CI 0.29–1.00). This absolute risk reduction of 19.8% translates to five patients requiring a year of treatment with pembrolizumab to prevent one cancer recurrence at two years. In patients without sarcomatoid features (n=829), patients randomized to pembrolizumab had improved DFS compared to placebo after 30 months of followup, although with lesser magnitude of benefit: 79.5% vs. 69.4%, respectively (HR 0.63, 95% CI 0.48–0.83). This absolute risk reduction of 10.1% translates to 10 patients requiring a year of treatment with pembrolizumab to prevent one cancer recurrence at 30 months.

#### ■ STATEMENT 8

**Patients with pT4 clear-cell RCC of any grade and those with N1 clear-cell RCC may be considered for adjuvant systemic therapy (consensus achieved: 100%).**

Patients with pT4 clear-cell RCC and those with N1 clear-cell RCC (Keynote-564 high-risk group) may be offered adjuvant systemic therapy with pembrolizumab. Patients in this group randomized to receive one year of pembrolizumab (n=40) had improved DFS compared to placebo (n=36) after 30 months of followup: 49% vs. 35%, respectively (HR 0.60, 95% CI 0.33–1.10). This absolute risk reduction of 14% translates to seven patients requiring a year of treatment with pembrolizumab to prevent one cancer recurrence at 30 months (NNT=7).

#### ■ STATEMENT 9

**Patients with resected M1 clear cell RCC and no evidence of disease (NED) may be considered for adjuvant systemic therapy (consensus achieved: 94%).**

Patients with resected M1 clear-cell RCC and NED may be offered adjuvant systemic therapy with pembrolizumab. In the Keynote-564 trial, this population was defined as those patients with M1 stage and no evidence of disease after complete resection of oligometastases synchronously or within one year of nephrectomy. Patients in this group randomized to receive one year of pembrolizumab (n=29) had improved DFS compared to placebo (n=29) after 30 months of followup: 78% vs. 38%, respectively (HR 0.28, 95% CI 0.12–0.66). This absolute risk reduction of 40% translates to three patients requiring a year of treatment with pembrolizumab to prevent one cancer recurrence at 30 months (NNT=3).

The panel noted that there were only 29 patients that met this clinical definition in each arm of Keynote-564. Some panelists felt that early recurrence in the M1 NED setting (i.e., after a period of active surveillance) may be better treated with a standard combination ICI-based therapy in the first-line metastatic setting (i.e., immuno-oncology [IO]/IO or IO/TKI) rather than offering earlier single-agent ICI adjuvant therapy. Some authors also acknowledged that adjuvant treatment may delay recurrence and the need for earlier combination systemic therapy, which may have patient-related and upstream healthcare implications. Overall, the panel concurs there is considerable uncertainty in this small subset of patients within Keynote-564 that had previously been offered surveillance.

#### ■ STATEMENT 10

**If patients receive adjuvant pembrolizumab, the duration of treatment should be one year (consensus achieved: 94%).**

The duration of therapy should follow the current evidence available from Keynote-564, where a one-year treatment protocol was used. In the real-world setting, there may be reasons for treatment interruptions or treatment cessation. The panelists felt that the collective duration of administered therapy offered should be one year, assuming it is clinically safe to do so. The authors acknowledged that alternative durations of therapy warrant future study, noting that a six-month duration of therapy in CheckMate 914 (albeit with nivolumab plus ipilimumab combination treatment) failed to demonstrate clinical benefit.



**■ STATEMENT 11**

If patients receive adjuvant therapy, followup imaging should be performed every 3–6 months during therapy (*consensus achieved: 100%*).

**■ STATEMENT 12**

On completion of adjuvant therapy, followup surveillance should continue per guidelines for localized disease (*consensus achieved: 100%*).

The panelists deliberated the most appropriate imaging assessments to accompany adjuvant therapy. Patients receiving adjuvant ICI therapy are routinely evaluated in medical oncology clinics. Imaging assessments in the Keynote-564 protocol were performed every 12 weeks in the first two years, every 16 weeks in years 3–5, and every 24 weeks thereafter (until the withdrawal of consent, disease recurrence, the start of new anticancer treatment, death, or the end of the trial, whichever occurred first); however, the panelists felt that in the real-world setting, patients on active therapy could have imaging performed every 3–6 months, bearing in mind patient and disease characteristics and noting that treatment would be administered for a duration of one year.

After completion of adjuvant therapy, the panelists felt recommended guidelines could be followed, accounting for having already been on ICI treatment for one year (i.e., surveillance start date remains date of surgery). Kassouf et al provide guidance on followup surveillance for non-metastatic RCC by intermediate-, high-, and very-high-risk pathological T-stage.<sup>12</sup> For patients who completed ICI therapy with no significant immune-related adverse events (irAEs), the panel felt followup could return to the urologist or urologic oncologist for standard surveillance; however, for patients who experience significant irAEs, followup should include continued care by a medical oncologist for ongoing monitoring for potential recurrence of irAEs. These decisions should be made in a shared-care setting with open lines of multidisciplinary communication.

**■ STATEMENT 13**

Patients who experience disease recurrence six months or more after completion of adjuvant therapy should be offered standard-of-care first-line treatment for metastatic disease (*consensus achieved: 100%*).

**■ STATEMENT 14**

Patients who experience disease recurrence during adjuvant therapy or within six months of completion should be treated similarly to patients who have progressed on first-line immunotherapy for metastatic disease (*consensus achieved: 100%*).

The use of standard first-line combination ICI (IO/IO or IO/TKI) for mRCC following adjuvant ICI was recently approved in Canada (after this consensus voting). Recurrence occurring six months or more after the completion of adjuvant therapy should be treated with standard first-line combination treatments for mRCC. In general, panelists suggested that care plans for patients who experience disease recurrence — while on or post-adjuvant ICI — should consider location and burden of recurrence, International Metastatic RCC Database Consortium (IMDC) risk group, and whether any further local therapy could be leveraged. Discussion at multidisciplinary case conferences would provide a meaningful avenue to select the optimal care plan.

For scenario #13, some panelists suggested that combination IO/IO (i.e., nivolumab plus ipilimumab) may be favored if patients are suitable and meet the criteria for use post-completion of adjuvant ICI;<sup>35</sup> however, outside of comparative data post-adjuvant ICI, the choice of a specific ICI-based combination should be discussed between the patient and physician. For scenario #14, panelists concurred that next-line treatment would follow standard mRCC recommendations post-prior ICI; for example, options would include any approved VEGF-TKI therapy as indicated.<sup>35</sup>

**DISCUSSION**

Treatments for patients with metastatic RCC have evolved tremendously in recent years, with new therapies achieving improved outcomes. This success has led to considerable excitement about the potential benefit of ICI-based therapies in the adjuvant setting post-surgery for patients with clear-cell RCC, with data from several randomized trials now available. To date, Keynote-564, which randomized patients to one year of adjuvant pembrolizumab or placebo, has reported improved DFS while several other ICI-based adjuvant trials have not reported a benefit.<sup>20</sup> Of note, patients with non-clear-cell or variant histologies of RCC were generally not included in the adjuvant trials.

Clinicians managing patients with RCC should be familiar with these data to properly counsel patients regarding the risks and benefits of adjuvant therapy. Considering these data, our panel believes urologists should discuss the risk of recurrence after surgery with patients based on pathological findings. Several tools

are available to help with risk stratification. Referral to medical oncology should be considered for eligible clear-cell RCC patients based on the Keynote-564 risk groups, given that treatment is now accessible in Canada.

### Interpretation of Keynote-564 in the context of all adjuvant clinical trials

Given that ICI-based adjuvant trials have not reported consistent results, it is important for clinicians to appreciate the limitations of the available studies, as well as possible explanations for the disparate results.<sup>21,22</sup> Important limitations of Keynote-564 include relatively short followup and evolving information regarding appropriate subsequent treatments received at the time of recurrence, which has implications for subsequent OS results.<sup>36</sup> Acknowledging the limitations of cross-trial comparisons with IMmotion 010 and CheckMate 914 (Part A), potential explanations for discrepant outcomes may also include: differences in the classification of patient populations, particularly in terms of defining intermediate-high-risk, definition and prevalence of M1 NED patients, prevalence of patients with sarcomatoid features, mechanism of agents studied (anti-PD-1 ± anti-CTLA-4 vs. anti-PD-L1 ICIs), necessary quantitative or qualitative tumor burden required for combination ICI benefit, duration of therapy (six months vs. one year), safety and tolerability, among other postulations. Pending data from ongoing trials, such as CheckMate 914 Part B (nivolumab) and RAMPART (durvalumab vs. durvalumab plus tremelimumab vs. active monitoring), are eagerly awaited.

### Overall survival

While DFS is an important clinical and regulatory approval endpoint, patients and clinicians are particularly interested in whether an intervention can meaningfully improve life span. This is particularly true when considering an adjuvant treatment because this therapy exposes many patients — who may never recur — to toxicity. Therefore, if patients who recur could achieve similar OS and quality of life outcomes with salvage therapy at the time of recurrence, this latter option may be more desirable for many patients.

The panelists strongly believe OS data should be closely followed and may ultimately determine if adjuvant therapy is widely adopted in Canada. Further, when interpreting OS data from Keynote-564, it is important to examine what therapy patients received at the time of disease recurrence. Patients enrolled in clinical trials of adjuvant therapy should receive the best available standard-of-care treatment on disease recurrence, which has important ethical and critical appraisal

implications.<sup>36</sup> At the last followup in Keynote-564, 17% of patients in the placebo arm vs. 12% in the pembrolizumab arm received subsequent VEGF-TKI treatment, and 12% vs. 3%, received subsequent ICI-based therapy, respectively.

### Risks of adjuvant immunotherapy

ICI-based therapy is generally well-tolerated when considering other available systemic treatments for mRCC; however, the risk tolerance profile in a palliative setting may be different than in an adjuvant setting, as a significant number of patients may never be destined for recurrence. When considering reported toxicities in Keynote-564, grade 3 or higher adverse events (AEs) were observed in 32% of patients in the pembrolizumab arm, compared to 18% in the placebo arm. AEs led to therapy discontinuation in 21% of patients receiving pembrolizumab vs. 2% in the placebo arm. High-grade immune-mediated AEs were 9% vs. 1%, and high-dose systemic corticosteroid treatment (defined as ≥40 mg per day) was required in 8% vs. 1%, respectively. While some adverse events are self-limiting or resolve with supportive treatments, others like thyroid disease and diabetes may expose the patient to lifelong morbidity and treatments to replenish endocrine dysfunction. Patients and physicians should carefully consider the risks of ICI treatment and balance them against potential benefits in a curative-intent clinical context.

### Future directions

Several questions remain in this rapidly evolving field. If adjuvant therapy is felt to be beneficial, determining the optimal duration of therapy is also vital. Based on Keynote-564, recommendations are for one year of therapy. Data reporting utility and tolerance of one year of adjuvant therapy in the real-world setting will be helpful to understand generalizability of trial results. Further, to what extent will adjuvant therapy affect the activity and efficacy of downstream treatments at the time of potential future recurrence? The Canadian Kidney Cancer Information Systemic (CKCis) and the IMDC may help us understand the effects of next-line access on the real-world experience of RCC patients who receive adjuvant ICI.

Future opportunities include adjuvant studies for the variant or non-clear-cell patient populations, the potential role of neoadjuvant treatment (beyond PROSPER-RCC), blood biomarkers or radiomics to potentially refine patient selection and understand microscopic disease clearance (i.e., cf/cfDNA), and longer-term followup for toxicity, as well as health-related quality of life metrics that are better tailored for the adjuvant setting.



## CONCLUSIONS

Patients with resected clear-cell RCC at increased risk of recurrence may derive benefit from ICI-based adjuvant systemic therapy. To date, adjuvant pembrolizumab is the only ICI agent shown to prolong DFS. Overall survival data for Keynote-564 remain immature at the time of this writing. Our panel believes eligible patients should be informed about adjuvant ICI therapy and offered referral to medical oncology to discuss the benefits and risks in a shared decision-making approach. Followup from completed trials and pending data from ongoing studies may help further refine the appropriate integration of ICIs in this setting.

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## REFERENCES

- Gupta K, Miller JD, Li JZ, et al. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): A literature review. *Cancer Treat Rev* 2008;34:193-205. <https://doi.org/10.1016/j.ctrv.2007.12.001>
- Richard PO, Violette PD, Bhindi B, et al. Canadian Urological Association guideline: Management of small renal masses - Summary of recommendations. *Can Urol Assoc J* 2022;16:24. <https://doi.org/10.5489/cuaj.7760>
- Bansal RK, Tanguay S, Finelli A, et al. Positive surgical margins during partial nephrectomy for renal cell carcinoma: Results from Canadian Kidney Cancer information system (CKCis) collaborative. *Can Urol Assoc J* 2017;11:182-7. <https://doi.org/10.5489/cuaj.4264>
- Psotka SP, Heidenreich M, Boorjian SA, et al. Renal fossa recurrence after nephrectomy for renal cell carcinoma: Prognostic features and oncological outcomes. *BJU Int* 2017;119:116-27. <https://doi.org/10.1111/bju.13620>
- Paparel P, Bigot P, Matillon X, et al. Local recurrence after radical nephrectomy for kidney cancer: Management and prediction of outcomes. A multi-institutional study. *J Surg Oncol* 2014;109:126-31. <https://doi.org/10.1002/jso.23473>
- Margulis V, McDonald M, Tamboli P, et al. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. *J Urol* 2009;181:2044-51. <https://doi.org/10.1016/j.juro.2009.01.043>
- Leibovich BC, Lohse CM, Chevillat JC, et al. Predicting oncologic outcomes in renal cell carcinoma after surgery. *Eur Urol* 2018;73:772-80. <https://doi.org/10.1016/j.eururo.2018.01.005>
- Leibovich BC, Blute ML, Chevillat JC, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: A stratification tool for prospective clinical trials. *Cancer* 2003;97:1663-71. <https://doi.org/10.1002/cncr.11234>
- Lam JS, Shvarts O, Leppert JT, et al. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. *J Urol* 2005;174:466-72. <https://doi.org/10.1097/01.ju.0000165572.38887.da>
- Kattan MW, Reuter V, Motzer RJ, et al. A postoperative prognostic nomogram for renal cell carcinoma. *J Urol* 2001;166:63-7. [https://doi.org/10.1016/S0022-5347\(05\)66077-6](https://doi.org/10.1016/S0022-5347(05)66077-6)
- Blackmur JP, Gaba F, Fernando D, et al. Leibovich score is the optimal clinico-pathological system associated with recurrence of non-metastatic clear cell renal cell carcinoma. *Urol Oncol Semin Orig Invest* 2021;39:438.e11-21. <https://doi.org/10.1016/j.urolonc.2021.04.007>
- Kassouf W, Monteiro LL, Drachenberg DE, et al. Canadian Urological Association guideline for followup of patients after treatment of non-metastatic renal cell carcinoma. *Can Urol Assoc J* 2018;12:231-8. <https://doi.org/10.5489/cuaj.5462>
- Levy DA, Slaton JW, Swanson DA, et al. Stage-specific guidelines for surveillance after radical nephrectomy for local renal cell carcinoma. *J Urol* 1998;159:1163-7. [https://doi.org/10.1016/S0022-5347\(01\)63541-9](https://doi.org/10.1016/S0022-5347(01)63541-9)
- Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal cell carcinoma after nephrectomy. *N Engl J Med* 2016;375:2246-54. <https://doi.org/10.1056/NEJMoa1611406>
- Haas NB, Manola J, Uzzo RG, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomized, phase 3 trial. *Lancet* 2016;387:2008-16. [https://doi.org/10.1016/S0140-6736\(16\)00559-6](https://doi.org/10.1016/S0140-6736(16)00559-6)
- Eisen T, Frangou E, Oza B, et al. Adjuvant sorafenib for renal cell carcinoma at intermediate or high risk of relapse: Results from the SORCE randomized phase 3 intergroup trial. *J Clin Oncol* 2020;38:4064-75. <https://doi.org/10.1200/JCO.20.01800>
- Ryan CW, Tangen C, Heath EI, et al. EVEREST: Everolimus for renal cancer ensuing surgical therapy — a phase 3 study (SWOG S0931, NCT01120249). *J Clin Oncol* 2022;40(17 suppl):LBA4500-LBA4500. [https://doi.org/10.1200/JCO.2022.40.17\\_suppl.LBA4500](https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA4500)
- Motzer RJ, Haas NB, Donskov F, et al. Randomized phase 3 trial of adjuvant pazopanib vs. placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. *J Clin Oncol* 2017;35:3916-23. <https://doi.org/10.1200/JCO.2017.73.5324>
- Gross-Goupil M, Kwon TG, Eto M, et al. Axitinib vs. placebo as an adjuvant treatment of renal cell carcinoma: Results from the phase 3, randomized ATLAS trial. *Ann Oncol Off J Eur Soc Med Oncol* 2018;29:2371-8. <https://doi.org/10.1093/annonc/mdy454>
- Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal cell carcinoma. *N Engl J Med* 2021;385:683-94. <https://doi.org/10.1056/NEJMoa2106391>
- Pal SK, Uzzo R, Karam JA, et al. Adjuvant atezolizumab vs. placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): A multicenter, randomized, double-blind, phase 3 trial. *Lancet* 2022;400:1103-16. [https://doi.org/10.1016/S0140-6736\(22\)01658-0](https://doi.org/10.1016/S0140-6736(22)01658-0)

22. Motzer RJ, Russo P, Grünwald V, et al. Adjuvant nivolumab plus ipilimumab vs. placebo for localized renal cell carcinoma after nephrectomy (CheckMate 914): A double-blind, randomized, phase 3 trial. *Lancet* 2023; Epub ahead of print. [https://doi.org/10.1016/S0140-6736\(22\)02574-0](https://doi.org/10.1016/S0140-6736(22)02574-0)
23. FDA approves sunitinib malate for adjuvant treatment of renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sunitinib-malate-adjuvant-treatment-renal-cell-carcinoma>. Accessed January 30, 2023.
24. Motzer RJ, Ravaud A, Patard JJ, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: Subgroup analyses and updated overall survival results. *Eur Urol* 2018;73:62-8. <https://doi.org/10.1016/j.eururo.2017.09.008>
25. Haas NB, Manola J, Dutcher JP, et al. Adjuvant treatment for high-risk clear-cell renal cancer: Updated results of a high-risk subset of the ASSURE randomized trial. *JAMA Oncol* 2017;3:1249-52. <https://doi.org/10.1001/jamaoncol.2017.0076>
26. Motzer RJ, Russo P, Haas N, et al. Adjuvant pazopanib vs. placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma: Final overall survival analysis of the phase 3 PROTECT trial. *Eur Urol* 2021;79:334-8. <https://doi.org/10.1016/j.eururo.2020.12.029>
27. Clark JI, Atkins MB, Urban WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: A cytokine working group randomized trial. *J Clin Oncol* 2003;21:3133-40. <https://doi.org/10.1200/JCO.2003.02.014>
28. Messing EM, Manola J, Wilding G, et al. Phase 3 study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma: an Eastern Cooperative Oncology Group/Intergroup trial. *J Clin Oncol* 2003;21:1214-22. <https://doi.org/10.1200/JCO.2003.02.005>
29. Powles T, Tomczak P, Park SH, et al. Pembrolizumab vs. placebo as post-nephrectomy adjuvant therapy for clear-cell renal cell carcinoma (KEYNOTE-564): 30-month followup analysis of a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23:1133-44. [https://doi.org/10.1016/S1470-2045\(22\)00487-9](https://doi.org/10.1016/S1470-2045(22)00487-9)
30. FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-pembrolizumab-adjuvant-treatment-renal-cell-carcinoma>. Accessed January 30, 2023.
31. CADTH Reimbursement Review. CADTH Reimbursement Recommendations - Pembrolizumab. Available at: [https://www.cadth.ca/sites/default/files/DRR/2022/PC0273\\_Keytruda\\_RCC\\_-\\_Confidential\\_Draft\\_CADTH\\_Recommendation\\_\(with\\_Corrections\\_Made\)\\_for\\_posting\\_September\\_1%2C\\_2022.pdf](https://www.cadth.ca/sites/default/files/DRR/2022/PC0273_Keytruda_RCC_-_Confidential_Draft_CADTH_Recommendation_(with_Corrections_Made)_for_posting_September_1%2C_2022.pdf). Accessed January 30, 2023.
32. Allaf M, Kim SE, Harshman LC, et al. Phase 3, randomized study comparing perioperative nivolumab (nivo) vs. observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. Available at: <https://oncolympo.esmo.org/meeting-resources/esmo-congress/phase-iii-randomized-study-comparing-perioperative-nivolumab-nivo-versus-observation-in-patients-pts-with-renal-cell-carcinoma-rcc-undergoing>. Accessed March 6, 2023.
33. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib vs. sunitinib for advanced renal cell carcinoma. *N Engl J Med* 2019;380:1116-27. <https://doi.org/10.1056/NEJMoa1816714>
34. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib vs. sunitinib for advanced renal cell carcinoma. *N Engl J Med* 2019;380:1103-15. <https://doi.org/10.1056/NEJMoa1816047>
35. Canil C, Kapoor A, Basappa NS, et al. Management of advanced kidney cancer: Kidney Cancer Research Network of Canada (KCRNC) consensus update 2021. *Can Urol Assoc J* 2021;15:84-97. <https://doi.org/10.5489/cuaj.7245>
36. Tannock IF, Goldstein DA, Ofer J, et al. Evaluating trials of adjuvant therapy: Is there benefit for people with resected renal cancer? *J Clin Oncol* 2023; Epub ahead of print. <https://doi.org/10.1200/JCO.23.00280>

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