

CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: Adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

ISSN: 2563-6596

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What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda should be reimbursed by public drug plans for the adjuvant treatment of adult patients with renal cell carcinoma (RCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients aged 18 years and older with RCC of clear cell subtype and previous nephrectomy, with or without surgery to remove 1 or more metastases, who are at intermediate-high or high risk of the tumour returning, and without prior systemic therapy for advanced RCC. Patients should also be in relatively good health.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed by a clinician with experience in RCC management, in specialized clinics with expertise in systemic treatment and immunotherapy delivery, and if the price of Keytruda is reduced. Keytruda should not be used in combination with other adjuvant cancer treatments.

Why Did CADTH Make This Recommendation?

Evidence from a clinical trial demonstrated that in patients with RCC who previously underwent nephrectomy, or nephrectomy with complete removal of metastases, those who were treated with Keytruda remained free of cancer for longer than those who were treated with placebo.

Keytruda is not considered cost-effective compared to routine surveillance alone. Economic evidence suggests that a 26% price reduction is needed to ensure Keytruda is cost-effective at a \$50,000 per quality-adjusted life-year (QALY) threshold.

Based on public list prices, Keytruda is expected to cost the public drug plans \$74,947,286 over 3 years.

Additional Information

What Is RCC?

RCC is a type of kidney cancer that begins from the lining of the kidney tubules. Nine out of 10 kidney cancers are RCCs. Clear cell RCC is the most common subtype of RCC, occurring in about 8 out of 10 people with RCC. Cancer staging is used by doctors to predict the likely course of the disease and make treatment decisions. In patients who are at risk of the cancer returning, additional treatment after surgery, known as adjuvant therapy, may be given to lower the chance of the cancer coming back.

Unmet Needs in RCC

There are no effective treatments available for patients with RCC in the adjuvant setting. Patients with RCC are in need of adjuvant treatment options with an acceptable toxicity profile that can improve health benefits.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately \$11,733 per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, only if the conditions listed in [Table 1](#) are met.

Rationale for the Recommendation

Evidence from 1 ongoing, phase III, double-blind, randomized controlled trial (KEYNOTE-564; N = 994) comparing the efficacy and safety of pembrolizumab with placebo for adjuvant treatment of adult patients with RCC after nephrectomy, or nephrectomy with complete resection of metastatic lesions, demonstrated that treatment with pembrolizumab (200 mg given every 3 weeks by IV infusion, for a total duration of 1 year) resulted in added clinical benefit with a statistically significant and clinically meaningful improvement in disease-free survival (DFS) (hazard ratio [HR] = 0.68; 95% CI, 0.53 to 0.87; P = 0.001) compared to placebo. The effect of adjuvant pembrolizumab on overall survival (OS) could not be determined due to the limitations associated with the immature survival data, and uncertainty on the effect of subsequent cancer therapies used in the trial. However, pERC agreed with the clinical experts that DFS is likely to be correlated with OS in the adjuvant setting, and that DFS itself is a meaningful outcome for patients with RCC in this setting.

Patients identified a need for effective adjuvant treatment options with an acceptable toxicity profile that could reduce the risk of disease recurrence, improve quality of life, and lengthen survival. pERC concluded that adjuvant therapy with pembrolizumab meets some of the needs identified by patients, including a need for effective treatments with manageable side effects and DFS benefit. pERC was unable to draw any conclusions on the effect of pembrolizumab on health-related quality of life (HRQoL) due to the exploratory nature of patient-reported outcomes in the trial, and a lack of established minimally important differences (MIDs) for HRQoL outcomes in the patient population of interest.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab was \$93,053 per QALY, compared with routine surveillance alone. At the sponsor-submitted price, pembrolizumab is not cost-effective at a \$50,000 per QALY willingness-to-pay (WTP) threshold for adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and complete resection of metastatic lesions. A reduction in price is required for pembrolizumab to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adjuvant treatment with pembrolizumab should only be reimbursed when initiated	Evidence from the KEYNOTE-564 trial demonstrated that pembrolizumab	*Intermediate-high risk, high risk, or M1 NED, defined by pathological

Reimbursement condition	Reason	Implementation guidance
<p>in adult patients who have all of the following:</p> <ol style="list-style-type: none"> 1.1. histologically confirmed diagnosis of RCC with a clear cell component, with or without sarcomatoid features 1.2. no prior systemic therapy for advanced RCC 1.3. intermediate-high risk or high risk of recurrence after nephrectomy, or M1 NED following nephrectomy and resection of metastatic lesions* 1.4. partial or radical nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion[s] in M1 NED participants) with negative surgical margins \geq 4 weeks before the initiation of treatment. 	<p>resulted in a statistically and clinically significant improvement in DFS in patients with characteristics listed in this condition.</p>	<p>tumour-node-metastasis, Fuhrman grading status, and presence of sarcomatoid features, as the following:</p> <p>Intermediate-high risk RCC:</p> <ul style="list-style-type: none"> • pT2, Grade 4 or sarcomatoid, N0, M0 • pT3, any grade, N0, M0 <p>High risk RCC:</p> <ul style="list-style-type: none"> • pT4, any grade, N0, M0 • pT any stage, any grade, N+, M0 <p>M1 NED RCC:</p> <p>Patients with a primary kidney tumour and solid, isolated, soft tissue metastases that could be completely resected at the time of nephrectomy (synchronous) or \leq 1 year from nephrectomy (metachronous)</p>
<p>2. Patients should have a good performance status.</p>	<p>No evidence demonstrating the benefit of adjuvant therapy with pembrolizumab in patients with an ECOG PS greater than 1 was identified. The KEYNOTE-564 trial included patients with an ECOG PS of 0 or 1.</p>	<p>Based on clinical expert input, selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.</p>
<p>3. Treatment with pembrolizumab should be initiated within 12 weeks of complete resection.</p>	<p>Evidence from the KEYNOTE-564 trial demonstrated that pembrolizumab resulted in significant clinical benefit in patients who receive the drug within 12 weeks after complete surgical resection.</p>	<p>—</p>
Discontinuation		
<p>4. Pembrolizumab should be discontinued upon the occurrence of any of the following:</p> <ol style="list-style-type: none"> 4.1. disease recurrence, defined as local recurrence of RCC, occurrence of distant metastases, or occurrence of a secondary systemic malignancy, determined by clinical, pathologic, and radiographic criteria 4.2. unacceptable toxicity 4.3. completion of 1 year of treatment (i.e., 17 doses for 200 mg or 9 doses for 400 mg, whichever 	<p>This condition is consistent with the criteria used for treatment discontinuation in the KEYNOTE-564 trial and the clinical practice.</p>	<p>—</p>

Reimbursement condition	Reason	Implementation guidance
is longer) in patients without disease recurrence.		
5. Patients should be assessed for disease recurrence, according to the criteria listed in Condition 4.1, every 3 to 6 months.	Clinical and imaging assessments for the KEYNOTE-564 trial were performed every 12 weeks (approximately every 3 months).	According to the clinical expert input, in clinical practice, patients would be assessed for disease progression every 3 to 6 months.
Prescribing		
6. Pembrolizumab should be prescribed by clinicians with experience and expertise in treating RCC. The treatment should be supervised and delivered in specialized clinics with expertise in systemic therapy and immunotherapy delivery.	Pembrolizumab should be prescribed only for appropriate patients and adverse effects should be managed in an optimized and timely manner.	—
7. Pembrolizumab can be continued for an equivalent of 1 year (12 months) of treatment, i.e., a maximum of either: 7.1. 17 cycles if administered at a dosage of 200 mg IV every 3 weeks, or 7.2. 9 cycles if administered at a dosage of 400 mg IV every 6 weeks.	The recommended dosage of pembrolizumab for the indication under review is 200 mg every 3 weeks or 400 mg every 6 weeks, until disease recurrence, unacceptable toxicity, or up to 1 year (12 months) or 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer. In the KEYNOTE-564 trial, patients were treated with pembrolizumab 200 mg every 3 weeks for a total treatment period of 1 year (i.e., 17 cycles).	The clinical experts noted that dosing of 400 mg every 6 weeks for up to 9 doses is commonly applied in clinical practice. Pembrolizumab may also be administered based on the patient's weight, at 2 mg/kg (up to a maximum of 200 mg) IV every 3 weeks, or 4 mg/kg (up to a maximum of 400 mg) IV every 6 weeks.
8. Pembrolizumab should not be reimbursed when used in combination with other adjuvant anticancer drugs.	Pembrolizumab was administered as monotherapy in the KEYNOTE-564 trial; no evidence demonstrating the safety and potential benefits of combining pembrolizumab with any other treatments was identified.	—
Pricing		
9. A reduction in price	The ICER for pembrolizumab is \$93,053 per QALY gained when compared with routine surveillance. A price reduction of at least 26% would be required for pembrolizumab to be able to achieve an ICER of \$50,000 per QALY, compared to routine surveillance.	—
Feasibility of Adoption		
10. The feasibility of adoption of pembrolizumab must be addressed.	At the submitted price, the budget impact of pembrolizumab is expected to be greater than \$40 million in year 3.	—

DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status; ICER = incremental cost-effectiveness ratio; M0 = no disease spread to distant organs; M1 = disease spread to other organs; mg = milligram; mg/kg = milligram per kilogram of body weight; N0 = no disease spread to lymph nodes; NED = no evidence of disease; pT2 = primary tumour > 7cm, limited to kidney; pT3 = primary tumour grown into major veins within the kidney or perinephric tissue; pT4 = primary tumour spread to areas beyond Gerota's fascia and extended into an adjacent organ; QALY = quality-adjusted life-year; RCC = renal cell carcinoma.

Discussion Points

- Based on the input from clinical experts and patients, pERC acknowledged the unmet need for an effective adjuvant therapy for kidney cancer to reduce the risk of disease recurrence and improve patient outcomes following nephrectomy, where the only option currently is post-operative surveillance.
- Improved quality of life was a need identified by patients. However, pERC was unable to make a definitive conclusion on the effect of pembrolizumab on patients' HRQoL due to the exploratory nature of patient-reported outcomes in the trial, substantial missing data on these outcomes, a lack of adjustment for multiplicity, and the lack of formally established MIDs.
- pERC highlighted the importance of patient-centred care, and noted that the choice to initiate adjuvant therapy should be based on shared decision-making and a discussion of clinical evidence on the available treatment options in the adjuvant setting, risks and benefits of treatment options, and the patient's informed preferences.
- The Health Canada recommended dosage for pembrolizumab in the patient population under review is 200 mg every 3 weeks or 400 mg every 6 weeks, until disease recurrence, unacceptable toxicity, or for a total treatment duration of 1 year (12 months; 17 doses for 200 mg or 9 doses for 400 mg), whichever is longer. pERC discussed that, although the pivotal trial used a 200 mg every 3 weeks dosing schedule, the 400 mg every 6 weeks and weight-based dosing schedules may be adopted by some clinicians in clinical practice to reduce burden on clinic resources and patients.
- Although the notable harms associated with pembrolizumab were appreciable in the KEYNOTE-564 trial, pERC agreed with the clinical experts consulted by CADTH that the safety profile of pembrolizumab observed in this study appeared to be in line with the known safety profile of immuno-oncologic therapy and considered to be manageable.

Background

In Canada, kidney and renal pelvis cancers were reported as the seventh most common cancers among males (5,200 new cases; 2.8% disease-related deaths) and the 12th most common among females (2,600 new cases; 1.7% disease-related deaths) in 2021. Almost 50% of kidney tumours are detected incidentally and many of them are asymptomatic. Classic symptoms (flank pain, visible haematuria, and palpable abdominal mass) are usually associated with more advanced disease stages as well as poorer prognosis. Around 65% of individuals are typically diagnosed while the tumour is confined to primary site (local disease), while a smaller proportion of patients are diagnosed when the tumour is spread to regional lymph nodes and metastatic sites (16% at regional and 16% at distant stages). Survival rates among patients with RCC largely depend on clinical factors such as tumour stage, grade, RCC subtype, presence of sarcomatoid features, local extent of tumour, presence of regional nodal metastasis, and evidence of metastatic disease at presentation. Estimated rates of 5-year metastasis-free survival among individuals with low, intermediate, and high Stage, Size, Grade and Necrosis (SSIGN) scoring risk are more than 95%, approximately 80%, and below 40%, respectively.

In Canada, the current standard of care for non-metastatic RCC is nephrectomy. Adjuvant treatment is not recommended in patients with non-metastatic RCC following nephrectomy, and current oncologic standard of care for these patients is observation.

Pembrolizumab has been approved by Health Canada for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. Pembrolizumab is a high affinity humanized monoclonal antibody that blocks the programmed cell death receptor 1 (PD-1) pathway. It is available as powder for solution for infusion 50 mg, and solution for infusion 100 mg/4 mL vial. The recommended dosage for pembrolizumab is 200 mg every 3 weeks or 400 mg every 6 weeks, administered as an IV infusion until disease recurrence, unacceptable toxicity, or up to 1 year (12 months) or 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer, in patients without disease recurrence.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 randomized, double-blind, phase III clinical study (KEYNOTE-564) in adult patients with RCC post-nephrectomy, or post-nephrectomy and resection of metastatic lesions
- patients' perspectives gathered by the Kidney Cancer Canada (KCC) patient group
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with RCC
- input from 2 clinician groups, including the Kidney Cancer Research Network of Canada and the Ontario Health Genitourinary Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One response to CADTH's call for patient input was received from KCC, which is a national community that provides support and education to patients living with kidney cancer and advocates for their care. The information used to inform the submission was based on 4 online surveys conducted by KCC in 2018 and March 2022, then in collaboration with the International Kidney Cancer Coalition (IKCC) in 2020, and by IKCC in May 2021. Direct input was also collected in March 2022 from 1 American patient with RCC who had experience with pembrolizumab. The 2018 survey supported a previous submission reviewed by CADTH by reporting on the challenges met by patients and caregivers living with kidney cancer. Among the 2,012 respondents of the 2020 international survey, 241 were living in Canada, of which 205 (85%) were patients with kidney cancer, 34 (14%) were caregivers, and 2 (0.8%) were undisclosed. A total of 141 patients with RCC responded to the 2021 survey. Among the 106 respondents to the 2022 survey, 65 (61%) patients and caregivers were living in Canada.

KCC reported that a large proportion of patients with RCC may eventually experience disease recurrence after nephrectomy leading to a substantially shortened life expectancy. The patient group input indicated that in the absence of adjuvant therapy options, patients with intermediate to high risk of recurrence experience anxiety and emotional distress from the expectation of recurrence and progression of disease. Nearly half (49%) of survey respondents indicated they would accept adjuvant immunotherapy if the therapy reduced the risk of disease recurrence by 40% to 50%. Approximately 50% of respondents indicated they would accept the risk of side effects associated with steroid use to manage the side effects of adjuvant immunotherapy if that level of risk is in the range of 20% to 25%.

According to the 1 patient who had experience with pembrolizumab in the adjuvant setting, the side effects of the treatment – including slight occasional rash, slight fatigue, and hyperkalemia – were manageable.

KCC emphasized that there is currently an unmet need for an effective adjuvant therapy for kidney cancer to reduce the risk of disease recurrence and improve patient outcomes, including a reduction in the number of patients who incur metastatic disease and the costs associated with RCC care.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Clinical experts consulted by CADTH emphasized that there is an unmet need among patients at a higher risk of recurrent disease after surgery for kidney cancer. Currently, there is no approved adjuvant treatment in this setting. The experts reported that pembrolizumab would be offered as a monotherapy in the adjuvant setting after resection of kidney cancer in patients at intermediate-high or high risk of recurrence. In the opinion of the clinician experts consulted, patients with clear cell carcinoma that have M1 resected metastases would benefit most from adjuvant treatment, followed by pT3-pT4 patient population (those at high risk of recurrence) and T2, grade 3 to 4 patient population (those at intermediate risk of recurrence). The experts identified patients with autoimmune diseases requiring steroids as those who should not receive adjuvant pembrolizumab. The clinical experts noted that OS and DFS represent important outcomes for the assessment of patient's response to treatment. Discontinuation of treatment was recommended by the clinical experts in case of disease recurrence or intolerable treatment toxicities. The experts reported that treatment administration and monitoring should be undertaken by a medical oncologist in an outpatient or community cancer setting.

Clinician Group Input

Two clinician groups provided input for this review: the Kidney Cancer Research Network of Canada and the Ontario Health Genitourinary Cancer Drug Advisory Committee. Two clinicians affiliated with the Kidney Cancer Research Network of Canada and 1 clinician on behalf of the Ontario Health Genitourinary Cancer Drug Advisory Committee contributed to this submission. The clinician groups agreed that there is an unmet need for adjuvant therapy to lower the risk of disease recurrence in patients with localized RCC following nephrectomy in Canada. The clinician groups indicated that, if funded, pembrolizumab would be the first adjuvant therapy option for patients with RCC in Canada.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
<p>There are no publicly funded comparators for the adjuvant treatment of intermediate-high risk to high risk RCC following nephrectomy, or following nephrectomy and resection of metastatic lesions. It is the understanding of PAG members that observation or enrolment on a clinical trial would be the usual practice in this setting.</p> <p>At the time of disease recurrence or evidence of metastatic disease, several drugs are publicly funded, including: pembrolizumab plus axitinib, ipilimumab plus nivolumab, nivolumab, sunitinib, pazopanib, sorafenib, axitinib, cabozantinib, and everolimus.</p>	<p>Clinical experts consulted by CADTH reported that there is currently no approved adjuvant treatment for patients with RCC at intermediate-high risk to high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, in Canada. pERC agreed with the clinical experts that the current standard of care in Canada for the patient population under review is “observation” or an enrolment in a clinical trial.</p>
Considerations for initiation of therapy	
<p>What stages and grades of RCC are eligible? What are the eligibility criteria or definitions for intermediate-high to high risk of recurrence?</p>	<p>pERC agreed with the clinical experts that eligibility of patients with RCC for adjuvant pembrolizumab treatment should be aligned with the inclusion criteria applied in the pivotal KEYNOTE-564 trial. Specifically, the following criteria should be applied:</p> <ul style="list-style-type: none"> • individuals with clear cell RCC, post-nephrectomy, who have intermediate-high risk for recurrence (pT2, Grade 4 or sarcomatoid, N0, M0; or pT3, any grade, N0, M0) • individuals with clear cell RCC, post-nephrectomy, who have high risk for recurrence (pT4, any grade, N0, M0; or pT any stage, any grade, N+, M0) • individuals who present with a primary kidney tumour and soft tissue metastases that could be completely resected either at the time of nephrectomy (synchronous) or ≤ 1 year after nephrectomy (metachronous).
<p>The KEYNOTE-564 study required treatment with pembrolizumab to be initiated within 12 weeks following surgery. What is the appropriate time frame following surgery to allow initiation of adjuvant pembrolizumab treatment in clinical practice?</p>	<p>Based on the information provided to CADTH by the sponsor, in the KEYNOTE-564 study, fewer than 50 (out of 994) trial participants initiated the study treatments more than 90 days after surgery. The clinical experts consulted by CADTH noted that, in the Canadian clinical setting, adjuvant pembrolizumab would be offered within 12 weeks post-nephrectomy in an effort to reduce a patient’s risk of recurrence. pERC agreed that the initiation of pembrolizumab within 12 weeks (3 months) after surgery is consistent with clinical practice and the adjuvant treatment initiation time frame in other indications.</p>
<p>Can immune checkpoint inhibitor therapy be given again to patients who relapse following completion of adjuvant pembrolizumab? What is the progression-free interval that</p>	<p>The clinical experts noted that, in the clinical practice, TKI agents (e.g., sunitinib, cabozantinib, pazopanib, or axitinib) are offered to patients who experience relapse while on adjuvant pembrolizumab</p>

Implementation issues	Response
<p>would be appropriate to reuse immune checkpoint inhibitor therapy? (Note: previous pERC recommendations that are followed by PAG members typically use a 6-month interval.)</p>	<p>treatment. The clinical experts believed that administration of ipilimumab/nivolumab or axitinib/pembrolizumab combination should be discouraged in these patients.</p> <p>pERC agreed with the clinical experts that patients who receive pembrolizumab in the adjuvant setting may be rechallenged or retreated with a PD-1 inhibitor combination (e.g., ipilimumab/nivolumab or axitinib/pembrolizumab), in the locally advanced or metastatic setting, if the patient experiences a disease recurrence after a disease-free interval of 6 months or more after completion of adjuvant therapy.</p>
<p>The KEYNOTE-564 trial enrolled patients with clear cell RCC histology. Would patients with non-clear cell histology who otherwise meet all eligibility criteria benefit from adjuvant pembrolizumab?</p>	<p>The eligibility criteria from the KEYNOTE-564 trial covered histologically confirmed diagnosis of RCC with clear cell component with or without sarcomatoid features by local review. pERC agreed with the clinical experts that there is insufficient evidence to support adjuvant treatment with pembrolizumab in patients with kidney cancers of histology other than clear cell.</p> <p>The clinical experts also noted that sarcomatoid features can occur in almost all types of RCC, and that sarcomatoid differentiation is not considered a unique histological subtype of RCC. Notably, presence of sarcomatoid features was considered as a predictor of poorer prognosis among patients with RCC, which suggests a need for adjuvant therapy, according to the clinical experts.</p>
Considerations for discontinuation of therapy	
<p>What criteria should be used to discontinue therapy?</p>	<p>pERC agreed with the clinical experts that treatment with pembrolizumab in adjuvant setting should be discontinued after 1 year of treatment (i.e., 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer) in patients without disease recurrence, in case of disease recurrence, or in case of intolerable treatment toxicities.</p>
<p>Pembrolizumab was administered in the KEYNOTE-564 study every 3 weeks for up to 17 cycles (approximately 1 year). If there are dose interruptions, should treatment be stopped at 1 year regardless of the number of doses administered, or could any “missed” doses be administered after the 1-year time period provided no disease progression has occurred? If so, what is the appropriate time period to complete the 17 doses (every 3 weeks cycle)?</p>	<p>pERC agreed with the clinical experts that treatment with adjuvant pembrolizumab can be administered until confirmed disease progression, unacceptable toxicity, or to a maximum of 17 doses (every 3 weeks), regardless of the time interval. Dose interruptions were permitted in the KEYNOTE- 564 trial for management of adverse events, situations such as medical or surgical events, or other logistical reasons. Patients could complete the remaining cycles of treatment upon resolution of adverse events or within 3 weeks of the scheduled interruption.</p>
Considerations for prescribing of therapy	
<p>In the KEYNOTE-564 study, pembrolizumab was administered every 3 weeks. However, the product monograph indicates that administration every 3 weeks or every 6 weeks is acceptable for other adjuvant use, even if clinical trials used a 3-week frequency (e.g., melanoma). Is it appropriate to implement a choice of every 3 week or every 6 week dosing regimens?</p> <p>PAG would like to inform pERC that they plan to implement</p>	<p>The experts believed that both 3-week and 6-week dosing schedules are appropriate. However, they noted that 400 mg every 6 weeks is more commonly used in clinical practice.</p> <p>Usually, patients would start with dosing of every 3 weeks and then switch to every 6 weeks once the treatment is shown to be well tolerated. Moreover, one of the experts stated that some Canadian provinces offer per-weight pembrolizumab dosing for metastatic RCC patients, which may lead to a lower than 200 mg</p>

Implementation issues	Response
<p>weight-based dosing up to the fixed dose for pembrolizumab – 2 mg/kg (up to 200 mg) every 3 weeks, and if the every 6 week regimen is recommended by pERC or approved by Health Canada, 4 mg/kg (up to 400 mg) every 6 weeks. (Note: at the time of PAG input, the product monograph and dosing information was not available.)</p>	<p>dose every 3 weeks, or a lower than 400 mg dose every 6 weeks, based on body weight.</p> <p>pERC agreed that the alternative 6-week cycle dosing schedule (400 mg doses up to 9 cycles) and weight-based dosing should be permitted.</p>
Generalizability	
<p>In the KEYNOTE-564 study, patients with ECOG PS 0 or 1 were eligible. Can patients with ECOG > 1 also be considered eligible?</p>	<p>pERC did not review any evidence to support the use of adjuvant pembrolizumab in patients with an ECOG PS higher than 1. However, the committee agreed with the clinical experts that selected patients with an ECOG PS of 2 could be considered for treatment at the discretion of the treating physician.</p>
Funding algorithm	
<p>The drug may change place in therapy of drugs reimbursed in subsequent lines.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
System and economic issues	
<p>The projected number of patients in Canada (excluding Quebec) starting pembrolizumab as a monotherapy in the adjuvant setting is 108 in the first year, increasing to 331 in year 2, and 456 patients in year 3, for a total of 895 patients over 3 years. At List Price, this represents a total 3-year cost of \$83,187,113 for pembrolizumab and an incremental cost of \$5,080,096 in the first year, \$25,018,568 in the second year and \$40,774,291 in the third year, for a 3-year net incremental cost of \$70,872,955.</p> <p>PAG is unsure if the market share assumptions for eligible patients (15% year 1, 45% year 2, 60% year 3) are appropriate, and therefore if patient estimates in the BIA model are accurate. If the market share assumptions are low, the patient numbers and subsequent BIA could be underestimated, resulting in affordability concerns. Additionally, if the manufacturer opens a compassionate PSP, sometimes there is a bolus of prevalent patients added to the incident patients in year 1 at the time of public funding, which may further result in an underestimate of the BIA for the first year.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>

BIA = budget impact analysis; ECOG PS = Eastern Cooperative Oncology Group performance status; M0 = no disease spread to distant organs; M1 = disease spread to other organs; mg = milligram; mg/kg = milligram per kilogram of body weight; NO = no disease spread to lymph nodes; NED = no evidence of disease; PAG = provincial advisory group; PD-1 = programmed cell death 1; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; PSP = patient support program; pT = tumour stage; pT2 = primary tumour > 7cm, limited to kidney; pT3 = primary tumour grown into major veins within the kidney or perinephric tissue; pT4 = primary tumour spread to areas beyond Gerota's fascia and extended into an adjacent organ; RCC = renal cell carcinoma; TKI = Tyrosine kinase inhibitors.

Clinical Evidence

Description of Studies

The KEYNOTE-564 trial (N = 994) is an ongoing, multi-centre, randomized, double-blind, phase III study with a primary objective to compare the efficacy and safety of pembrolizumab versus placebo as an adjuvant treatment for adult patients with RCC post-nephrectomy, or post-nephrectomy and resection of metastatic lesions. The trial was conducted in 212 sites across 21 countries, including Canada. The study enrolled patients who were 18 years of age and older with a histologically confirmed diagnosis of RCC with a clear cell component, with or without sarcomatoid features. The study included patients at intermediate-high risk or high risk of recurrence, based on pathological tumour-node-metastasis staging, Fuhrman grade, and presence of sarcomatoid features, and patients following metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients were also required to be tumour-free, have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and have no prior systemic treatment for RCC. The primary outcome investigated in the KEYNOTE-564 trial was DFS, assessed by the investigator. The key secondary outcome was OS; other secondary outcomes included disease recurrence specific survival (DRSS), event-free survival (EFS) assessed by blinded independent radiology review, safety, and HRQoL.

Patients were randomized in a 1:1 ratio to receive either pembrolizumab (200 mg IV infusion every 3 weeks; N = 496) or placebo (saline solution IV every 3 weeks; N = 498) for up to a maximum of 17 infusions or (approximately) 1 year, until confirmation of recurrence, treatment discontinuation, or study termination. Randomization was stratified based on the metastasis status variable (M0 versus M1 NED). Within the M0 group, randomization was further stratified according to the following factors: ECOG PS (0 or 1) and US participant (Yes or No). By the time of the first interim analysis (IA) (December 14, 2020), 1,406 patients were screened and 994 were randomized into the trial (496 in pembrolizumab and 488 in placebo arm). One additional analysis (the Efficacy Update Report [EUR]) was implemented after 6 additional months of follow-up, with a cut-off date of June 14, 2021.

The median age of patients enrolled in the KEYNOTE-564 study was 60 years, with the majority of participants being White (over 75%) and male (over 70%) in both treatment groups. Most patients had tumours with an absence of sarcomatoid features and belonged to the intermediate-high recurrence risk category. Baseline characteristics were equally balanced in the 2 study arms. More patients discontinued treatment in the pembrolizumab arm (38.9%) compared to the placebo arm (26.2%), primarily due to adverse events (AEs). More patients in the placebo arm (22.5%) received subsequent systemic anticancer treatment compared to the pembrolizumab arm (15.3%).

Efficacy Results

Overall Survival

At the first IA data cut-off (December 14, 2020), the median follow-up durations were 24 months (range = 2.5 to 41.5) and 23.8 months (range = 3.5 to 41.4) for patients in pembrolizumab and placebo groups, respectively. The median OS was not reached in either treatment arm. An HR of 0.54 (95% CI, 0.30 to 0.96; P = 0.0164) was estimated for the comparison between pembrolizumab and placebo. Additional 6-month follow-up data from

the EUR analysis (June 14, 2021 data cut-off) showed that the median OS was not reached in both groups, with an observed HR of 0.52 (95% CI, 0.31 to 0.86; P = 0.005).

DFS, Assessed by Investigator

Similarly, median DFS was not reached in both treatment groups at the time of the first IA (December 14, 2020). The HR obtained between the pembrolizumab versus placebo was 0.68 (95% CI, 0.53 to 0.87; P = 0.001). Results from the EUR analysis, with a data cut-off of June 14, 2021, demonstrated an HR of 0.63 (95% CI, 0.50 to 0.80; P < 0.0001). Median DFS was not reached in either group at the time of the EUR.

According to the pre-specified subgroup analysis, the HRs for the DFS across the metastatic staging groups was 0.74 (95% CI, 0.57 to 0.96) for the M0 group and 0.29 (95% CI, 0.12 to 0.69) for the M1 NED group. Similar findings were observed in the EUR analysis, with 6 additional months of follow-up (for the M0 subgroup: HR = 0.68; 95% CI, 0.53 to 0.88; for the M1-NED subgroup: HR = 0.28; 95% CI, 0.12 to 0.66). EUR results of the post hoc subgroup analysis according to the recurrence risk showed the following estimates: 0.68 (95% CI, 0.52 to 0.89), 0.60 (95% CI, 0.33 to 1.10), and 0.28 (95% CI, 0.12 to 0.66) for the intermediate-high risk, high risk, and M1-NED risk groups, respectively.

Health-Related Quality of Life

HRQoL assessments included the overall least squares mean difference estimated for the pembrolizumab versus placebo arms. Among patients completing the HRQoL measures, patients in both arms appeared to experience slight deterioration in HRQoL and symptom worsening assessed at week 52. The overall least squares mean difference in the FKSI-DRS score was -0.67 (95% CI, -1.23 to -0.12). The least squares mean difference in the EORTC QLQ-C30 questionnaires was -2.57 (95% CI, -5.22 to 0.08) for global health status/quality of life and -0.91 (95% CI, -2.79 to 0.97) for physical function.

Harms Results

The proportion of patients with at least 1 treatment emergent AE appeared higher in the pembrolizumab arm (96.3%) than in the placebo group (91.1%). Serious AEs were reported among 20.5% of individuals who received pembrolizumab treatment, compared to 11.3% of individuals receiving placebo. There were more AEs leading to drug discontinuations (pembrolizumab versus placebo: 20.7% versus 2.0%) and treatment interruptions (25.8% versus 14.9%) in the pembrolizumab arm compared to placebo. Overall, 2 deaths were reported in the pembrolizumab arm (0.4%), and 1 death was reported in the placebo arm (0.2%).

Notable harms were higher in the pembrolizumab group than in the placebo group. Hyperthyroidism (21.1% versus 6.9%), hypothyroidism (11.9% versus 0.2%), pneumonitis (2.3% versus 1%), adrenal insufficiency (2% versus 0.2%), type 1 diabetes mellitus (1.8% versus 0%), colitis (1.6% versus 0.2%), severe skin reactions (1.6% versus 0.4%), infusion reactions (1.4% versus 1%), thyroiditis (1.2% versus 0.2%), and hepatitis (1% versus 0%) were the notable harms observed in the pembrolizumab and placebo arms, respectively.

Critical Appraisal

The KEYNOTE-564 trial is an ongoing, multi-centre, randomized, placebo-controlled, double-blind study. The randomization scheme implemented in the trial minimized the risk of bias due to unknown confounders. Owing to a placebo-controlled design, potential for unblinding

might have occurred due to higher frequencies of immune-related AEs in the pembrolizumab arm, compared to the placebo arm. Baseline and demographic characteristics were balanced in the 2 study arms, suggesting successful randomization. Concomitant medications permitted in the trial, as well as subsequent anticancer therapies administered, were considered appropriate by the clinician experts consulted by CADTH and reflective of treatments used in Canadian practice.

OS, DFS, and HRQoL investigated in the trial were considered clinically meaningful outcomes by the clinician experts and reflective of outcomes assessed in clinical practice. Other surrogate end points, such as DRSS and EFS, were considered of lower clinical relevance, according to the clinical experts.

The primary outcome (DFS) was assessed by the local investigators, and BICR assessments were introduced to evaluate the robustness of the DFS findings. Findings of DFS by BICR were consistent with the primary analysis, suggesting low possibility of evaluation bias. Multiplicity adjustments were implemented adequately for the analysis of DFS and OS, and sensitivity analyses were also pre-specified and conducted for DFS. The findings from the sensitivity analyses were consistent with the primary intention-to-treat (ITT) analyses. Median DFS and OS were not reached at the time of conducted interim analyses, suggesting data immaturity. More patients in the placebo arm received post-treatment anticancer therapies compared to the pembrolizumab arm, which might have produced biased estimates of OS (favouring the placebo group). Of note, surgery in patients with RCC is performed with a curative intent, and 5-year disease specific survival is lengthy in patients at intermediate risk (about 80%) and high risk of recurrence (from 40% to 55%) post-nephrectomy. Hence, longer follow-up is needed to observe the effects of adjuvant pembrolizumab on survival outcomes. The findings from the analysis of secondary and exploratory outcomes (EFS, DRSS, HRQoL) as well as defined subgroups were considered exploratory, as no multiplicity adjustments were performed. The magnitude of effect of pembrolizumab on HRQoL of patients in the adjuvant setting is uncertain due to lack of formal hypothesis testing, possible violation of missing data assumptions in the model applied, and low attrition rates.

There were several interim analyses pre-specified in the protocol before the first IA (December 14, 2020), which was used as the base for this CADTH report. Another IA (i.e., EUR) with 6 months of additional follow-up data was added in between the first and second IA to respond to potential requests from regulatory agencies. The final OS analysis will take place after approximately 200 deaths are observed between the pembrolizumab and placebo groups. Adjustments were made to account for alpha spending across the interim analyses.

The clinician experts consulted by CADTH for this review reported that the baseline characteristics and the findings of the KEYNOTE-564 can be generalizable to adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions, in the Canadian setting. The administered dosage of pembrolizumab was 200 mg every 3 weeks for up to 17 doses, which is aligned with the pre-NOC Health Canada indication. The clinical experts noted that dosing of 400 mg every 6 weeks for up to 9 doses is more commonly applied in real clinical practice. Appropriateness of the placebo as the comparator was confirmed by the clinical experts, as there are no Health Canada-approved adjuvant treatment options available in Canada. According to the clinical experts, patients recruited in the pivotal trial had more frequent disease assessments and follow-up procedures compared to what would be applied in patients in real-world practice.

Conclusions

One sponsor-submitted, multi-centre, randomized, double-blind, phase III trial (KEYNOTE-564), comparing adjuvant therapy with pembrolizumab to placebo in patients with RCC, was included in this CADTH systematic review.

Overall, pembrolizumab improved DFS outcomes, compared to placebo, as an adjuvant treatment of patients with RCC who are at intermediate-high or high risk of recurrence after nephrectomy, or following nephrectomy and resection of metastatic lesions. However, the effects of adjuvant pembrolizumab relative to placebo on OS could not be determined because of the immature survival data, uncertain influence of subsequent treatments, and uncertainty in the correlation between DFS and OS in adjuvant treatment of RCC. Likewise, limitations with the HRQoL analyses in the single randomized controlled trial (RCT) precluded drawing conclusions about the effects of pembrolizumab on this outcome. The safety profile of pembrolizumab was similar to that observed in other trials of this drug, including the effects on the thyroid and adrenal glands. The clinician experts considered the baseline characteristics and the findings from the KEYNOTE-564 trial generalizable to patients with RCC in the adjuvant setting in Canada.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions
Treatment	Pembrolizumab
Submitted price	Pembrolizumab, 100 mg, solution: \$4,400.00 per 100 mg/4 mL vial
Treatment cost	\$11,733 per 28 days
Comparator	Routine surveillance alone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (41.6 years)
Key data source	KEYNOTE-564 trial
Key limitations	<ul style="list-style-type: none"> • DFS and OS data were not mature in both groups by the data cut-off (June 14, 2021). The sponsor assumed a relationship between DFS and OS based on a retrospective data study, but other studies in the literature did not find strong correlation between the 2 outcomes. As the association between the 2 outcomes is not established, it is uncertain whether benefits in DFS would translate into benefits in OS in actual practice. • The sponsor assumed the benefit of pembrolizumab would be sustained indefinitely after 1 year of treatment with pembrolizumab in terms of DFS and OS. According to clinical experts consulted by

Component	Description
	<p>CADTH for this review and the sponsor’s analysis of the Kaplan-Meier curves, the impact of adjuvant pembrolizumab on long-term DFS or OS (especially once the 1-year treatment period is completed) is uncertain for adjuvant treatment of intermediate-high risk and high risk RCC.</p> <ul style="list-style-type: none"> • The submitted model did not consider the possibility of cure following nephrectomy, which is not aligned with the disease pathway, according to clinical experts. • The submitted model overestimated the survival of patients experiencing distant metastasis. • The sponsor applied RDI in the derivation of the costs for pembrolizumab and subsequent therapies. This is inappropriate as RDI can be influenced by many different factors.
CADTH reanalysis results	<ul style="list-style-type: none"> • CADTH undertook reanalyses to address limitations relating to uncertainty regarding persistence of treatment effect; lack of the possibility of cure after nephrectomy; underestimation of the survival of patients who develop metastatic recurrence; and use of RDI. • In CADTH base case, for the proposed Health Canada indicated population, pembrolizumab was associated with an ICER of \$93,053 compared to routine surveillance (inc. costs = \$79,750; inc. QALYs = 0.86). • For pembrolizumab to be cost-effective compared to routine surveillance at a willingness-to-pay threshold of \$50,000 per QALY, a price reduction of 26% is required.

DFS = disease-free survival; incr. = incremental; ICER = incremental cost-effectiveness ratio; LY = life-year; mg = milligram; mL = millilitre; OS = overall survival; QALY = quality-adjusted life-year; RDI = relative dose intensity.

Budget Impact

CADTH identified the following key limitations: the referral rate to oncologists may be underestimated, the assumption regarding patient enrolment in clinical trials as a comparator is inappropriate, and the use of relative dose intensity (RDI) may not accurately capture treatment costs.

CADTH’s base case revisions included: increasing the referral rate to oncologists, revising the proportion of patients who were assumed to be in clinical trials to 0%, setting RDI to 100%, and using a weight-based pembrolizumab dose. CADTH also explored uncertainty in the market uptake estimates, wastage and dose of pembrolizumab, and incident case distribution throughout the year.

Based on the CADTH’s base case, the expected budget impact for funding pembrolizumab for the adjuvant treatment of intermediate-high risk and high risk RCC in the drug plan perspective is expected to be \$5,452,069 in Year 1, \$26,377,162 in Year 2, and \$41,832,259 in Year 3, with a 3-year budget impact of \$73,661,491.

Results of CADTH’s scenario analyses demonstrate that the estimated budget impact is highly sensitive to the changes in dosing and wastage.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane,

Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: August 9, 2022

Regrets: Of the expert committee members, 2 did not attend.

Conflicts of interest: None