CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

pembrolizumab (Keytruda RCC)

(Merck Canada Inc.)

Indication: Renal cell carcinoma, adjuvant

September 16, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0273-000
Brand name (generic)	Keytruda (pembrolizumab)
Indication(s)	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.
Organization	Kidney Cancer Research Network of Canada (KCRNC)
Contact information[a]	Name: Maria Komisarenko, KCRNC Manager [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

KCRNC has reviewed Table 1. Reimbursement Conditions and Reasons Table 1 and believe the conditions for treatment initiation, discontinuation and prescribing are generally reasonable. However, in recognition of current pressures on the Canadian healthcare system, treating physicians (and patients) would benefit if the window of treatment initiation was extended from 12 weeks to 16 weeks:

> While pembrolizumab offers an effective and well-tolerated adjuvant therapy for patients with surgically resected RCC at high-risk of disease recurrence, patients with resected RCC represent a heterogeneous population and there is no perfect tool to predict disease recurrence. Thus optimal patient selection will require thorough clinical assessment which may include post-nephrectomy imaging and a pathology re-review.
>
> Furthermore, treating physicians will need to take special care to inform patients that the toxicities from pembrolizumab are not negligible. Given that patients being treated in the adjuvant setting are, by definition, cancer symptom–free at the onset of treatment, careful consideration as to potential short- and long-term toxicities of treatment must be taken into account. While a shared decision-making approach with regards to treatment decision-making for RCC is standard practice, the thoughtful application of adjuvant IO therapy will require detailed discussions with the patient, and the patient should not be rushed into the decision.
>
> While clinical assessment and shared decision-making can both consume much time, patients in rural areas may also need to be referred to a cancer centre for assessment and counseling. Recognizing that referrals and subsequent appointment can take weeks, and with the additional pressures on wait times caused by COVID19, hospitals and treating physicians may not be able to accommodate the 12 week window in all cases.

While treating physicians will most certainly seek to initiate patients on adjuvant therapy within 12 weeks of complete resection, the various clinical considerations, health system pressures and decision-making complexities may require an expanded window of time for some patients.

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
If not, what aspects are missing from the draft recommendation?		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 Dr. Nawar Hanna • Clinician 2 Dr. Anil Kapoor • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Nawar Hanna*
Position	*Clinician 1 – Associate Professor CIUSSS*
Date	*21-09-2022*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Knight Therapeutics	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

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Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0273-000
Brand name (generic)	Pembrolizumab (Keytruda)
Indication(s)	Adjuvant treatment of adult patients with RCC at intermediate-high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
Organization	Ontario Health (CCO) Genitourinary Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Aly-Khan Lalani

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
The DAC agrees with the clinician expert reviewers that if disease free 6 months or more after completing adjuvant therapy, patients could be re-challenged with IO based combination first line therapy. The limitations extrapolating to nccRCC histologies are reasonable for now, given emerging data.		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
Ontario Health provided secretariat functions to the DAC.		
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Aly Khan Lalani		

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0273
Name of the drug and Indication(s)	Pembrolizumab for adjuvant RCC
Organization Providing Feedback	PAG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
None.
b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

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Stakeholder information	
CADTH project number	PC0273-000
Brand name (generic)	Keytruda (Pembrolizumab)
Indication(s)	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.
Organization	Kidney Cancer Canada
Contact information[a]	Christine Collins, Executive Director, Kidney Cancer Canada [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Extend window of treatment initiation from 12 to 16 weeks

While Kidney Cancer Canada (KCC) generally agrees with the recommendation, we do encourage CADTH to modify the reimbursement criteria to reflect current realities in healthcare, and accommodating patient needs, by extending the window of initiation of treatment with pembrolizumab from 12 to 16 weeks.

Rationale:

1. Patients need appropriate time for informed, shared decision making at an RCC specialist centre. This could include the need for adequate discussion at cancer centres re: alternative options, including close observation and clinical trials in the adjuvant setting. Additionally, consideration of side effects, from the patients perspective is extremely important. While most side effects of immune checkpoint inhibitors (ICI) are short-lived (acute) and can be treated with steroid drugs, the potential for long-term or chronic side effects of immunotherapy is significant and patients require ample time to consult with a physician (who has experience with the use of immune checkpoint inhibitors) to make this decision.

2. Patient Selection is key. Identifying patients appropriate for adjuvant therapy is complex. Medical Oncologists need adequate time to determine, with the patient, if a patient should be initiated on adjuvant treatment. This may include any required imaging post-nephrectomy with an urologist/uro-oncologist (especially if pre-surgery imaging was not optimal). There also may be time needed for a pathology re-review.

3. Canadian RCC patients include many in rural/remote areas who will require travel coordination to expert centres. This is perhaps unique in RCC (vs other cancers) because patients are often surgically treated in their communities with local urologists. Many of these

patients have not yet entered a cancer centre. For these patients the opportunity to meet with a physician experienced in both treating RCC and experienced in prescribing ICIs (perhaps by way of referral) can take many weeks. We point to the International Kidney Cancer Coalition (IKCC) IKCC Global Survey in 2020 (Canada n=232) were 35% of respondents indicated that "Wait Time for Treatment" was the most referenced barrier to accessing quality care, followed by "No specialty doctor locally" (22%).

4. Delays in accessing cancer care and appointments with oncologists is not limited to patients in rural/remote areas. At the moment, COVID-19 has created tremendous stress to our health system causing patients to experience tremendous delays in accessing care/appointments.

5. While data for other cancers is mixed on the optimum timing for initiation of adjuvant therapy, for RCC, an additional 4-week delay before treatment initiation will likely not make a clinical difference in outcomes but will make a significant difference in practical terms for the patient and caregiver in the Canadian healthcare context. Notably, an eligible group of patients in the KEYNOTE 564 trial who benefited from adjuvant therapy are those who had resectable soft tissue metastases at diagnosis (M1 stage disease) in addition to the primary renal tumour. These patients were initiated on adjuvant treatment up to one year following nephrectomy and continued to show a benefit in disease-free survival.

Non-Clear Cell RCC

KCC believes that patients diagnosed with non-clear cell RCC should NOT be excluded from the opportunity to access adjuvant treatment with pembrolizumab. Under the current reimbursement guidance, these patients will be left with zero options in the adjuvant setting -- and there will likely be no Phase 3 trials given the rarity of these subtypes.

Non-clear cell RCC patients have fewer treatment options, and worse survival than those with clear cell.

Note: technically, the KN-564 trial included patients that: *Has histologically confirmed diagnosis of renal cell carcinoma (RCC) with clear cell component with or without sarcomatoid features* (clinicaltrials.gov)

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification. While the implementation issues have been clearly articulated, we urge CADTH to modify the implementation criteria as per our recommendation in section 1.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
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- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	***Christine Collins – Kidney Cancer Canada Assoc.***
Position	***Executive Director***
Date	***September 15, 2022***
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☐
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☐

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
BMS	☐	☐	☒	☐
Eisai	☐	☐	☒	☐
Ipsen	☐	☐	☐	☒
Merck			☒	
Novartis		☒		
Pfizer				☒