CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

pembrolizumab (Keytruda)

(Merck Canada Inc.)

Indication: First-line treatment of locally advanced unresectable or metastatic, carcinoma of the esophagus or HER-2 negative gastroesophageal junction adenocarcinoma in combination with platinum and fluoropyrimidine based chemotherapy, in adult patients.

November 18, 2021

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0250-000
Brand name (generic)	Keytruda (pembrolizumab)
Indication(s)	First-line treatment of locally advanced unresectable or metastatic, carcinoma of the esophagus or HER-2 negative gastroesophageal junction adenocarcinoma in combination with platinum and fluoropyrimidine based chemotherapy, in adult patients.
Organization	OH-CCI GI Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Erin Kennedy [redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale. Improved PFS, OS; agree with funding for the overall population Agree with using with different chemo backbone including FOLFOX, CAPOX Agree with imaging every 8-12 weeks Agree with a maximum of 35 administrations Siewert classification of 1 should be left at treating clinician's discretion (vs specifying 1 to 5 cm above the gastric cardia)		

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.		

Siewert classification of 1 should be left at treating clinician's discretion (vs specifying 1 to 5 cm above the gastric cardia)		
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.
- 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.

A. Patient Group Information	
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 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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

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		
2. 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. OH-CCO provided secretariat support for the DAC.		
3. Did you receive help from outside your clincian 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		
4. 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. Erin Kennedy • Dr. Jim Biagi • Dr. Christine Brezden-Masley • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Tim Asmis*
Position	*Medical Oncologist*
Date	*15-Nov-2021*
☒	**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**
Merck – local PI for Merck (no personal payment)	☐	☐	☐	☐
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
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	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0250
Name of the drug and Indication(s)	Pembrolizumab for Esophageal carcinoma, gastroesophageal junction adenocarcinoma
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	x
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
In Table 1. Reimbursement Conditions and Reasons, under the heading “Renewal”, PAG is requesting the following revision, “In Keynote 590, a benefit of pembrolizumab was observed for up to 24 months (*i.e.,* completion of 35 administrations).”

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
In the Discussion Points section, in the fourth bullet, PAG is requesting the following deletion of the text “pERC encouraged jurisdictions to make PD-L1 CPS testing available to help identify patients who may experience the greatest benefits from pembrolizumab.”

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0250
Brand name (generic)	KEYTRUDA® (pembrolizumab)
Indication(s)	KEYTRUDA®, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2 negative adenocarcinoma of the esophagogastric junction (tumour centre 1 to 5 centimetres above the gastric cardia).
Organization	Merck Canada Inc.
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.		
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	☒
Some conditions included in the draft recommendation depart from precedents set by past recommendations. As such, Merck respectfully requests that these conditions be modified to align with previous evaluations. First, condition #2 is not aligned with previous pCODR recommendation on KEYTRUDA® for the first-line treatment of metastatic cancers, where eligibility was not restricted to patients not previously treated with anti-PD-1/anti-PD-L1 agents. More precisely, for the review of KEYTRUDA® in 1L NSCLC (Project Number: PC0153-000) pERC considered the CGP's expert opinion and agreed that, for patients who received prior adjuvant or consolidation durvalumab and remain candidates for platinum-		

pemetrexed chemotherapy, it would be reasonable to consider treatment with platinum-pemetrexed plus pembrolizumab. This was recommended while durvalumab was also under review for locally advanced, unresectable NSCLC in patients whose disease has not progressed following platinum-based chemotherapy.

It is also important to emphasize that provincial reimbursement criteria for KEYTRUDA® and other anti-PD-1/anti-PD-L1 agents across various tumors currently allow previously anti-PD-1/anti-PD-L1 treated patients to have access to the drug in the metastatic setting if the previous agent was received for an earlier disease stage. Implementing condition #2 as stated would depart from current practices:

• Ontario Health (Cancer Care Ontario): NSCLC patients who were treated with durvalumab (or other anti-PD-1/anti-PD-L1 therapy) in the curative setting and have a disease-free interval of 6 months or greater after completion of treatment can be considered to receive pembrolizumab for advanced/metastatic disease.[1]

• For the treatment of patients with unresectable or metastatic melanoma in Ontario, “patients whose disease relapses at least 6 months after completing adjuvant anti-PD-1 inhibitor may be eligible for combination ipilimumab and nivolumab in the metastatic setting or, if the patient is unfit for combination immunotherapy, single agent immunotherapy.”[1]

• For the treatment of patients with unresectable or metastatic melanoma in Alberta, anti PD-1/anti-PD-L1 agents “May be used after adjuvant nivolumab or pembrolizumab if relapse is equal to or greater than 6 months from completion of that adjuvant therapy.”[2]

• For the treatment of patients with unresectable or metastatic melanoma in British Columbia, patients are eligible for anti-PD-1/anti-PD-L1 agents if relapse is greater than 6 months of completing adjuvant anti-PD1 therapy.[3]

Moreover, the Clinical Review Report (Pg. 28) stated that “considerations should be given to patients treated by adjuvant nivolumab and in their subsequent lines of therapy in the metastatic setting”. The draft recommendation, however, does not reflect this consideration. If the draft recommendation was to be applied with condition #2 as currently stated, this would also introduce inequity for patients with locally advanced unresectable or metastatic carcinoma of the esophagus or HER2 negative adenocarcinoma of the esophagogastric junction compared to patients with other tumors as noted above.

Due to equity considerations for patients, considerations by treating clinicians, and to ensure consistency across pCODR recommendations and reimbursement criteria, Merck respectfully requests that pERC consider that patients who received prior adjuvant therapy with an anti PD-1, anti PD-L1 or anti-PD-L2 should remain candidates for pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy.

Second, to ensure alignment with the language used in the rest of the draft recommendation and avoid confusion, Merck also kindly requests that the wording “pembrolizumab in combination with platinum and fluoropyrimidine based chemotherapy” be used instead of “cisplatin and 5-FU” in conditions 1-2-3-6.

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

References

[1] pembrolizumab | Cancer Care Ontario
[2] https://www.albertahealthservices.ca/assets/programs/ps-1025651-drug-benefit-list.pdf
[3] http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Melanoma/SMAVPEM_Protocol.pdf