CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

PEMBROLIZUMAB AND LENVATINIB (Keytruda and Lenvima)

(Merck Canada Inc.)

Indication: Keytruda in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

August 18, 2022

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0288-000
Brand name (generic)	Pembrolizumab and Lenvatinib (Keytruda and Lenvima)
Indication(s)	Keytruda in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.
Organization	Ontario Health (CCO) Gynecology Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Sarah Ferguson

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.

- Health Canada has approved pembrolizumab single agent for dMMR endometrial cancer. Since the CADTH review resulted in a negative recommendation, there will not be public funding. There is a treatment gap for the dMMR population which were included in the KEYNOTE-775 trial in a significant number as part of the overall population. The response rate was highest in the dMMR patient subgroup in the trial. The DAC feels strongly that the current recommendation for pembrolizumab and lenvatinib should be reconsidered to include dMMR patients, as dMMR patients rely strongly on compassionate programs.

- [In reference to Table 2: the guidance on the maximum number of prior lines of platinum therapy] The DAC felt that this should not be limited to patients who received multiple lines of platinum-based chemotherapy who otherwise met the trial eligibility criteria. The DAC suggests revising to include patients who received multiple prior lines of chemotherapy (including non-platinum chemotherapy). The DAC recognizes that this patient population that are progressing on multiple lines of platinum-based chemotherapy will be quite small.

- [In reference to Table 2: time-limited funding] The DAC suggests that patients who are currently on treatment should be allowed to switch to the pembrolizumab and Lenvatinib regimen on a time-limited basis at the discretion of the treating physician and in discussion with the patients regardless of whether they are experiencing toxicity. The DAC recognises that this patient population will be quite small and will diminish over time.

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	☒
Ontario Health provided secretariat function 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	☐
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: • Dr. Sarah Ferguson		

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0288
Name of the drug and Indication(s)	pembrolizumab and lenvatinib for advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR)
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, PAG is requesting the following revisions:

- Under the "Implementation Guidance" heading, adding the text "*pERC agreed with the clinical experts consulted by CADTH that the results of the KEYNOTE-775 trial could be generalized to patients with multiple prior lines of platinum-based chemotherapy who otherwise met the trial's eligibility criteria."*
- In 1.2, replacing regimen with "*for advanced disease*"
- Under the heading "Discontinuation" in the "Implementation Guidance" column, rewording the text to "*It would be reasonable to re-administer pembrolizumab at the time of relapse (up to 17 additional every 3 week doses or 1 year), with or without lenvatinib, at the discretion of the treating physician for patients who previously discontinued pembrolizumab before any disease progression or disease progression occurred during a treatment break."*

3. Clarity of the recommendation
Complete this section if editorial revisions are requested for the following elements

a) Recommendation rationale

In Table 3 Cost and Cost-effectiveness, in the treatment row, PAG is requesting adding the dosing schedule and pricing of Lenvatinib.

b) Reimbursement conditions and related reasons
None.
c) Implementation guidance
None.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PCO288-000
Brand name (generic)	Pembrolizumab + Lenvatinib
Indication(s)	For the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy and are not candidates for curative surgery or radiation.
Organization	**Colorectal Cancer Resource & Action Network** (CCRAN) in collaboration with **Canadian Cancer Survivor Network** (CCSN)
Contact information[a]	Name: Filomena Servidio-Italiano [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.

While we were pleased with the recommendation, we do wish to include the following for your kind consideration:
Page 4, Reimbursement Condition #2: "*Patient must not have either of the following:*

a. MSI-H
b. dMMR disease

…MSI/MMR status must be determined prior to initiating treatment to ensure patients do not have MSI-H or dMMR disease (i.e. pMMR or MSS)."

We wish to provide two comments in respect of biomarker identification:

i. In order to initiate treatment, the above recommendation clearly states that the patient must <u>not</u> be identified to have MSI-H or dMMR disease. For the <u>untested patient</u>, however, who has progressed on platinum based first line systemic treatment (and there will be patients whose MSI/MMR status will not have been determined early on in their care path depending upon where they reside in Canada), this should not preclude the patient from proceeding to access the combination therapy in a most timely fashion. Once the patient accesses the combination therapy, should testing identify them to have dMMR or MSI-H disease, the Lenvatinib portion of the treatment protocol can most certainly be removed at that point in time, allowing them to continue with the Pembrolizumab monotherapy. Our interviewed patients have emphatically expressed a need to proceed to therapy in a most timely manner, avoiding any delays in treatment that can potentially compromise outcomes.

ii. In the event a patient's test result returns an "<u>*indeterminate*</u>" finding, perhaps allowances can be considered for this patient, allowing them to proceed to the combination therapy. Indeterminate findings account for an extremely small percentage of test results,

	demonstrating inconclusive biomarker status. Nevertheless, advanced endometrial cancer patients want to avail themselves of a protocol that can help to reduce their disease, which may include the combination therapy. If a repeat test is administered, and an MSI-H/dMMR status is determined, then once again, the Lenvatinib portion of the protocol may certainly be removed from the combination therapy and the patient may continue with the pembrolizumab monotherapy. As previously described, the goal is to ensure timely access to therapy, as echoed by interviewed and surveyed 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? Yes. Additionally, we were delighted to see that the ECOG performance status was expanded to include ECOG 2. Thank you!		
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 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	***Colorectal Cancer Resource & Action Network (CCRAN)*** ***Filomena Servidio-Italiano***
Position	***President & CEO***
Date	***14-08-2022***
☒	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**
Merck	☐	☐	☐	☒