CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

pembrolizumab (Keytruda)

(Merck Canada Inc.)

Indication: Keytruda for Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy

June 16, 2022

Centre universitaire de santé McGill

McGill University Health Centre

To the CADTH Reimbursement Review Committee members:

The gynecologic and medical oncologists of the McGill University Health Centre would like to share their concern over CADTH's recent decision to not recommend reimbursement for pembrolizumab for the treatment of MMR deficient/MSI-high advanced or metastatic endometrial cancer.

It is our understanding that the recommendation is based on the lack of a randomized controlled trial where the comparator arm would consist of chemotherapy.

Historically, responses to chemotherapy in this patient population have been low and short-lived, especially after failure of a platinum-based regimen. Response rates in recurrent endometrial cancer to chemotherapy do not surpass 27%.[1]

With the advent of immune checkpoint inhibitors and suitable predictive bio makers, we are seeing more profound and durable responses in women with endometrial cancer.

This seems to be a class effect. Both Keynote 158 and a similar trial, GARNET, with dostarlumab have demonstrated response rates of 48% and 43.5%, respectively [2,3]. Furthermore, in Keynote-158, the median overall survival has not been reached after a follow-up of 42.6 months[4].

In our own practice, we've been able to access pembrolizumab for our patients dMMR endometrial cancer that is metastatic or advanced through the patient support program. We have seen complete responses, not seen with chemotherapy. Moreover, we have seen *durable* responses, not seen with chemotherapy.

This is not unique to endometrial cancer. This is a class effect which has been reproduced in a tumour agnostic way based on biomarkers, such as with the Keynote-177 trial which showed superiority of pembrolizumab in advanced/metastatic colorectal cancer[5]. In addition, there is plausible concern that these tumours may be more chemotherapy resistant[6,7]. Given the excellent responses with immune checkpoint inhibitors in this population and the possibility of poorer response to chemotherapy, a randomize trial would never be ethical.

For these reasons, we ask you to reconsider your initial recommendation and allow women with this devastating disease to have access to the best therapy possible in the era of precision medicine.

Sincerely,

[redacted]

Victoria Mandilaras, MDCM, FRCPC
On behalf of the Gynecologic Oncology Team
Cedars Cancer Centre
McGill University Health Centre, Montreal, Quebec

References

[1] Bradford, Leslie S.; Rauh-Hain, Jose Alejandro; Schorge, John; Birrer, Michael J.; Dizon, Don S. *American Journal of Clinical Oncology* 38(2):206-212, April 2015.

[2] Marabelle A, Le DT, Ascierto PA, et al. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol.* 2020;38(1):1-10.

[3] Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET—a phase I, single-arm study *Journal for ImmunoTherapy of Cancer* 2022;10:e003777

[4] O'Malley D, Bariani GM, Cassier PA, et al. Pembrolizumab (pembro) in patients (pts) with microsatellite instability-high (MSI-H) advanced endometrial cancer (EC): Updated results from KEYNOTE-158. Presented at: European Society for Medical Oncology (ESMO) Congress 2021; September 16-21, 2021. Abstract 795MO.

[5] André T, Shiu K, Kim TW, et al. Pembrolizumab in Microsatellite-Instability–High Advanced Colorectal Cancer. *N Engl J Med*. 2020; 383(23): 2207-18

[6] Brown R, Hirst GL, Gallagher WM, McIlwrath AJ, Margison GP, van der Zee AG, Anthoney DA. hMLH1 expression and cellular responses of ovarian tumour cells to treatment with cytotoxic anticancer agents. *Oncogene* 1997; 15:45-52.

[7] Alex AK, Siqueira S, Coudry R, et al. Response to chemotherapy and prognosis in metastatic colorectal cancer with DNA deficient mismatch repair. *Clin Colorectal Cancer*. 2017;16:228–39.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0280-000
Brand name (generic)	Pembrolizumab (Keytruda)
Indication(s)	Keytruda for Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.
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	☐

1) Rare tumors and small patient populations are not adequately acknowledged with CADTH's processes.

A lower level of evidence should be accepted for a patient population with a rare tumour type that has no other treatment options. The magnitude and duration of benefit seen in the clinical trial for pembrolizumab is dramatic and not seen in this patient population with second line chemotherapy. It is unlikely that we will see a higher level of evidence in this group of patients with rare tumours and where the population size is small. Additionally, other drugs in the same class are also being investigated as single arm study with significant benefits. By not acknowledging this data in tumors that are not common, there will continue to be a lack of option for these patients.

2) There are inequities within CADTH's processes for patients with rare cancers.

The DAC raises concerns around potential inequitable access to pembrolizumab for MIS-H/dMMR endometrial cancers. Because this is a Health Canada approved indication, patients with the means to pay out-of-pocket or with private insurance may still be able to access this drug. Additionally, the DAC raises concerns around inequities with the investigation in rare cancers as these patients are insufficiently studied by clinical trials. CADTH's negative recommendation highlights the limitations and inequities in their processes when it comes to rare cancers.

3) Regulatory approval in larger jurisdictions

There is already regulatory/funding approval in larger jurisdictions (UK, US, and Europe). As a result, there is no motivation by the drug companies to fulfill CADTH's expectation of higher level of evidence for this drug-indication, especially since Canada represents a small global market share. Also, investigation-initiated studies are unlikely because of the high drug cost.

Patients are aware that these drugs are approved by Health Canada. Patients are asking for these drugs to be available and many do not have the means to pay for them. They are aware that other jurisdictions have funding approval and this leads to Canadian patients to have inequitable access to these drugs.

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	☒
N/A ("Do not reimburse"); implementation issues are not addressed as a result		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒
N/A		

[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	☐
No.		
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 • Dr. Stephen Welch • Dr. Orit Freedman • Dr. Taymaa May • Dr. Julie Francis • Dr. Leah Jutzi • Dr. Josee-Lyne Ethier		

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0280
Brand name (generic)	Keytruda (pembrolizumab)
Indication(s)	Pembrolizumab for adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.
Organization	Alberta Gynecologic Oncology Group
Contact information[a]	Name: Prafull Ghatage

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

Based on Keynote 158 I believe that Pembro showed meaningful antitumor activity. 48% had an objective response with manageable SAEs. The median duration of response was not reached after a follow up of 42.6 months. It is estimated that >60% of patients will have a response of 5.3 years.

These patients have a dismal prognosis and the use of Pembro allows for an opportunity to improve on PFS.

The study by Kelkar et al on a multicenter retrospective chart review from the USA showed that there was a positive impact on the use of Pembro in MSI-H/dMMR patients.

It has now become the standard of care in the USA for patients who have progressed following systemic chemotherapy.

This also applies to Europe where the EMA has approved its use in MSH-H and dMMR patients after having failed systemic chemotherapy.

Expert committee consideration of the stakeholder input		
	Yes	☐

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	No	☐
If not, what aspects are missing from the draft recommendation? N.A		
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

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- 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.
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- 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	☒
Presentations at SGO, ESGO, ESMO,GOC used to collect information. In addition we have listened to multiple presentations on this top[ic.		

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 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*PRAFULL GHATAGE*
Position	*Gyn oncologist, Calgary. Gyn Oncology Tumor Group lead for Alberta*
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 2	
Name	*Jeanelle Sabourin*
Position	*Head of Gyn Oncology, Edmonton. Tumor Group lead for Cross Cancer Institute,Edmonton.*
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	*Gregg Nelson*
Position	*Head of gyn Oncology, Tom Baker Cancer Centre, Calgary.*
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Dr Helen Steed*
Position	*Gyn Oncologist,* Facility Medical Director, CCI, Associate Senior Medical Director, CCA Zone Clinical Department Head Oncology
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	PC0280
Brand name (generic)	Pembrolizumab
Indication(s)	MMRd/MSI-H endometrial cancer
Organization	BC Provincial Gynecologic Cancer Tumour Group
Contact information[a]	Name: Anna Tinker

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

The pERC has conducted a very thorough review of the clinical evidence.

However, we believe the committee has not adequately contextualized that data. Our tumour group requests that pERC consider these additional points:

1) The mechanism of action of immune-checkpoint inhibitors across multiple cancers with MMRd/MSI-H.
2) The updated PFS and OS Kaplan-Meier curves, in particular the plateau observed at 2 years from the Keynote-158 study using pembrolizumab
3) A negative decision on funding will leave Canadian women with no effective treatment options and Canada out of step with the rest of the world

1) Immune-checkpoint inhibitors (ICIs) have been repeatedly demonstrated to be highly effective in tumours harboring high tumour mutational burden, in particular MMRd/MSH-I cancers. All tumours defined by this molecular biomarker have a high probability of benefiting from ICIs. Randomized data have been easier to obtain in more prevalent cancer types such as MMRd colon cancers where the benefits have been clearly demonstrated. This is a pan cancer effect and MMRd endometrial cancers are no different with high levels of efficacy demonstrated in single arm phase 2 setting with ICIs. Beyond platinum-based chemotherapy in recurrent, metastatic MMRd/MSI-H endometrial cancer there is no standard of care and therefore no known effective treatment with which to compare immune checkpoint inhibitors to, making a randomised controlled clinical trial wholly unethical, and phase 2 data in this sub-type adequate to change standard of care.

2) KN-158 study demonstrates an exceptionally high activity level of pembrolizumab and durable clinical benefits in a biomarker selected population. The PFS and OS KM survival curves of the KN-158 trial demonstrate a plateauing of both curves starting at 2-years, and ~50% of patients have ongoing long term cancer control and maintaining quality of life.

Among known therapies for endometrial cancer, no other has demonstrated this KM survival curve pattern, not even at lower benefit rates. Historical trial data do not include molecular classification of endometrial cancer by MMR status, as molecular classification was only introduced in 2014. However, if there had been a subset of the patient population (e.g. MMRd/MSI-H) who were benefiting from the treatments under study, then long-term stability of a small proportion of cases should have been observed (i.e. some tail on the curve, if only in a low percentage of cases). No such observations exist.

3) While it is understood that the lack of a comparator treatment may limit the ability of CADTH to definitively quantitate the magnitude of benefit of pembrolizumab in this molecularly defined patient subgroup, this does not negate the significant clinical benefit observed and should not be a basis on which to deprive Canadian women of this highly effective treatment. The current negative decision means Canadian women with MMRd/MSI-H endometrial cancer are likely to be out-survived by their peers globally. To put in other words, approximately 40-60 patients per year in Canada will lose the opportunity to receive this life extending treatment.

For the first time there is a therapy with a validated, low cost biomarker for a treatment that gives the possibility of excellent long term outcomes. The "do not reimburse" decision will leave Canadian women with metastatic MMRd/MSI-H endometrial cancer without access to effective therapy as currently available Patient Support Programs will close.

Given that the principle that 'ICIs work in MMRd/MSI-H endometrial cancer' is now widely accepted as already proven globally by FDA, EMA, NICE, oncologists and pharma alike it is unlikely that further clinical trials will ever be done in this space. This will lead to denying even women who can access trials (this in itself raises issues of equity) alternative opportunities to get access to these effective treatments

Most current trials have moved on to investigate ICIs in the adjuvant setting of MMRd/MSI-H endometrial cancers, thus women with recurrent or metastatic disease will not be eligible.

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	☐

The reasons are stated, and they are clear, but they are not properly contextualized, following old processes for new paradigms.

The old processes miss the mark on highly active therapies with unprecedented benefits, in biomarker defined populations, with well understood underlying mechanisms of action linked directly to disease biology, this is precision medicine at its best and the need for comparator is outdated These older processes favor the funding of less effective agents simply because they were studied in a phase 3 setting and to do this here would put patients at risk.

Failing to act to implement biomarker-defined treatments, when all evidence is consistent with a biomarker-driven benefit, is a breach of faith between the research community and patients who have volunteered for trials. We have persuaded patient participants to partner in tumour-agnostic trials, and then are not applying new models of trial design or analysis despite new models of patient selection. This is particularly egregious where we have studied an already well-understood, readily available, and relatively safe drug type. We cannot afford to replicate phase 3 trials across all types of organ-defined cancer, and so where do we draw the line? Who will we leave on the sidelines, with rare cancers and a biomarker of interest, likely to signal a consistently good chance of benefit, simply

because a traditional phase 3 trial is not feasible or economic to mount? We need to consider the FDA drug approval of new drugs in a tumour agnostic situation, because beyond that point, the incentive for pharma to fund large phase 3 trials declines sharply, along with the ethics of doing such studies. Having demonstrated a very significant potential benefit based on biomarker expression, our efforts and research dollars should be going not toward trying to prove this over and over in each individual tumour type, but in trying to improve further on these results, via drug combinations or other explorations.

pERC is clearly concerned about precedent setting decisions that may impact future reviews, however, there will be few situations for which all of the points above could be made beginning with a clear understanding of biology, mechanism of action, and unprecedented clinical outcomes. This is a very unique situation which must be considered in the context of all of the above.

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	☐

Additional data will be forthcoming but will be in the adjuvant or first-line setting, leaving any woman with MMRd/MSI-H recurrent endometrial cancer who is facing progression on standard therapy or recurrence after first-line chemotherapy without access to this highly active treatment, a treatment that all of us would want if we were to find ourselves in that position. Current options provide very minimal benefit to patients with a high burden of toxicity. The decision to not reimburse would result in inequality of care and poor outcomes for these patients who are in need of highly effective treatments.

We must also consider the impact a do not reimburse decision would have in the context of equity. A number of patients due to their social circumstances (background, English not being their first language, rural/underserved community, etc) will be unable to access pembrolizumab, due to limited financial means or lack of available clinical trial options and will therefore be receiving sub standard care resulting in a shortened survival. This will result in the creation of two different groups of patients: those who are fortunate vs. those with limited means, a situation that is not consistent with Canadian values.

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

Appendix 2. Conflict of Interest Declarations for Clinician Groups

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- 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.		
3. 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		
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: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Anna Tinker*
Position	*Medical Oncologist, BC Provincial Tumour Group Chair, Gynecologic Oncology*
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 patient 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**
GSK	☐	☒	☐	☐
AZ	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Merck	X			

New or Updated Declaration for Clinician 2	
Name	*Aalok Kumar*
Position	*Medical Oncologist, BC Provincial Systemic Chair, Gynecologic Oncology*
Date	*June 14, 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**
GSK	☐	☒	☐	☐
Pfizer	☒	☐	☐	☐
Merck	☒	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Yvette Drew*
Position	*Medical Oncologist, BC Cancer Vancouver*
Date	*June 14, 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**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Susan Ellard*
Position	*Medical Oncologist, BC Cancer Kelowna*
Date	*June 14 ,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**
MERCK	☐	☒	☐	☐
AZ	☒	☐	☐	☐
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 6	
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	PC0280
Name of the drug and Indication(s)	Pembrolizumab for MSI-H or dMMR endometrial cancer
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.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0280-000
Brand name (generic)	Pembrolizumab (KEYTRUDA)
Indication(s)	For the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy
Organization	Canadian Cancer Society
Contact information[a]	Name: Sasha Frost [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.

The recommendation did not align with the advanced endometrial patient perspectives captured within the joint submission completed by CCRAN, CCSN and CCS.

- Advanced endometrial cancer is experiencing a significant unmet need for new treatment options. Current treatments for advanced endometrial cancer are associated with treatment induced toxicities that compromise quality of life and often fail to extend patients' longevity in a meaningful way. Interviews, testimonials, and survey responses from patients underscored these severe side effects and a strong need for more effective treatment options.
- To reiterate some of our key findings, four patients provided detailed input on their experience with pembrolizumab. Three participated in an interview, and one in a survey. All four patients expressed a significant need to improve therapeutics for the management of advanced endometrial cancer due to the limited number of treatment options. All three interviewed patients indicated the therapy under review was easier to use when compared to previously administered therapies and claimed it resulted in an improved quality of life. For patients who accessed Pembrolizumab + Lenvatinib, patients appreciated the opportunity to access an oral therapy (Lenvatinib) which is easily administered in the comfort of their own homes. Patients also appreciated the short infusion time associated with Pembrolizumab which was administered every 3 weeks, unlike the infusion times associated with previously administered standard of care therapies for advanced endometrial cancer (Carbotaxol and Doxorubicin). Two of the three interviewed patients struggled with cancer induced symptoms prior to starting the therapy under review, and in each case the therapy provided significant resolution of those symptoms. Efficacy was radiographically and clinically confirmed in each patient's case (with the exception of Patient C who was scheduled to undergo imaging within a few weeks of their telephone interview, but the patient was confident that based on how they were feeling clinically and based on their recent lab results, that efficacy would be confirmed in CT scan findings).

- Overall, patients expressed the desire to access pembrolizumab free of charge and had hope others would have the opportunity to access this drug as well. One example of this sentiment was expressed in the following quote: "I couldn't afford to pay for this on my own, so I am so terribly appreciative of this. This therapy is my hope for a great extension in life. It is my way of continuing to live. Is it going to change for me? Will I be able to accept it for free in the future? I am so scared I might run out of luck in that respect and be forced to pay for it which is why I am participating today. I pray that I will be able to accept this therapy for free and that others who qualify will be able to accept it for free as well so they can benefit like me."

Overall, due to the strong patient perspectives collected through surveys, interviews and testimonials, it can be concluded that the outcome of this deliberative process does not reflect the preferences of the patients who participated in providing feedback.

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?

The recommendation did include a summary of patient perspectives captured within the patient submission, however, the focus of the rational for the recommendation was largely focused on clinical trial structure and results. More clarity on the weight patient perspectives carry in the deliberative process would be helpful in determining the degree in which patient perspectives were considered.

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.

More information regarding the rationale for a "do not reimburse" recommendation over a "reimburse with conditions" recommendation would clarify the outcome of the deliberative process. Due to the significant unmet need this population is experiencing and the strong support expressed within the patient submission, it would be helpful (particularly if patients inquire) to better understand why patients with no other treatment options should not be able to access/try this medication if certain conditions were met despite some uncertainty in the clinical trial results.

[a] CADTH may contact this person if comments require clarification. Contact information will not be included in any public posting of this document by CADTH.

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	*Sasha Frost*
Position	*Sr Advocacy Specialist (Patient Engagement)*
Date	*16-06-2022*
☒	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. Details from the initial submission which included data collected by CCRAN and CCSN was utilized in this feedback.		

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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0280-000
Brand name (generic)	Keytruda (Pembrolizumab)
Indication(s)	Keytruda for Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.
Organization	**Colorectal Cancer Resource & Action Network (CCRAN)** In collaboration with the Canadian Cancer Survivor Network (CCSN)
Contact information[a]	Name: **Filomena Servidio-Italiano, President & CEO, CCRAN** [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.

We respectfully yet strongly disagree with the committee's recommendation based on the following:

1. There is an urgent, unmet need for the MSI-H/dMMR metastatic endometrial cancer patient population given their poor prognosis, high symptom burden, and extremely limited treatment options. Pembrolizumab would surely help to address this important therapeutic need, as there are currently no targeted treatments available for MSI-H/dMMR metastatic endometrial cancer patients.
2. (Page 3, Rationale for the Recommendation, last paragraph: "***…it is uncertain whether pembrolizumab meets these needs given the limitations associated with the evidence reviewed.***") Our patient input clearly highlighted the need for treatments that improve endometrial cancer symptoms, improve quality of life, have a manageable side effect profile, improve patients' longevity, provide greater daily independence, delay disease progression, and improve long term remission. **Our patients who accessed the therapy under review emphatically expressed, based on their experience with the therapy, that Pembrolizumab met most of, if not all, these criteria, as highlighted in the submission. While limited in numbers, the evidence provided in the patient input submission cannot be ignored nor can the experiential testimonials provided be ignored, for they speak to the preferences, values and priorities of the patients who dedicated considerable time and effort relaying the most intimate and challenging journey of their life.**
3. (Page 8, 4[h] paragraph, Critical Appraisal: "***The main limitation of the included pivotal study KN-158…..***"): We are mindful of the study's limitation: a single-arm design, which precluded a definitive comparison with outcomes with standard of care therapies. We feel compelled, however, to point out that there is no acceptable, satisfactory standard of care second line treatment in this setting and, as such, the overall response rate in the KN-158

was quite robust when compared with chemotherapeutic agents in second line therapy, which have been associated with dismal response rates in patients diagnosed with recurrent/metastatic MSI-H/dMMR endometrial cancer. The data generated in this Phase II study was nevertheless impressive and cannot be disregarded for a **small subset** of the population who is identified to have a unique mutation, and whose mutation should be treated in a targeted manner.

4. (Page 10, Budget Impact) According to the 2022 projected stats (CCS), 8100 cases of endometrial cancers will be diagnosed in 2022. Approximately 25% of women diagnosed with endometrial cancer will be diagnosed with advanced disease and 20% will have a recurrence of the disease. Approximately 25-31% of patients with endometrial cancer (all stages) have tumours with high levels of MSI-H/dMMR (Journal of Clinical Oncology 40, no. 7, March 1, 2022, 752-761) and 13-30% of recurrent/metastatic endometrial cancers are MSI-H/dMMR (*Makker, et al., DOI https://doi.org/ 10.1200/EDBK_ 280503*). This certainly supports economic feasibility seeing that a rather small subset of the endometrial cancer patient population qualifies for the therapy under review, helping to fill that *urgent, unmet need in the MSI-H/dMMR patient population*.

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?

(Page 8, Critical Appraisal, Second paragraph, "***As all results are part of an interim analysis…..")*** CCRAN feels quite privileged to provide the patient and caregiver perspective as a means of informing the HTA deliberative process. As a result of having expanded our mandate to now include patient input submissions for patient groups who do not have the capacity to perform these submissions **or** for therapeutic sites wherein there is no representative patient advocacy group, we believe we are filling a gap. Some of these therapeutic areas, however, such as the MSI-H/dMMR advanced endometrial cancer population represent a challenging and somewhat "*rare*" cancer. This subset of the endometrial cancer patient population has a poor prognosis, respond poorly to chemotherapeutics, have no satisfactory second line treatments, and have a mutation that has NOT to date been addressed from a targeted therapy perspective. While there is a deliberative framework in place for 'rare cancers', the MSI-H/dMMR endometrial cancer patient population has much in common with a rare disease: they have a truly severe illness and an urgent unmet need. And, as such, perhaps this kind committee can permit a greater allowance of uncertainty in the review of this therapy. Seeing there is no acceptable or satisfactory second line therapy, requesting phase III evidence would be somewhat problematic for patients. We kindly request you reconsider your recommendation in light of this information and plea, as well as the above noted information provided.

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.

(Page 8, Critical Appraisal) While the recommendation was articulately relayed, we would like to comment on the following:
Phase I/II evidence has indeed served as the basis for a conditional positive funding recommendation as recently as April 2022 for Selpercatinib (Retevmo), in the treatment of metastatic RET fusion-

positive non small cell lung cancer (NSCLC). We are, of course, delighted for this patient population and see many similarities between that study and the current KN-158 study. Both were non-randomized, non-comparative, open-label studies with relatively small sample sizes offering a lack of formal hypothesis testing. It too served as a basket trial with a unique biomarker for patients who also have no satisfactory standard of care therapies. Based on the review, the follow up duration time was not quite as long as that for the KN-158 study.

We wish to propose that the same review lens that was offered for Selpercatinib in RET fusion-positive NSCLC be offered for Pembrolizumab and MSI-H/dMMR advanced endometrial cancer. This would surely promote equity and consistency in CADTH's funding recommendations across the various tumour types and the patient populations who stand to benefit extensively from those recommendations.

We hereby kindly request a reconsideration of the negative funding recommendation issued for Pembrolizumab for the treatment of adult patients with unresectable/metastatic MSI-H/dMMR endometrial cancer, as monotherapy.

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.

N/A

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.

N/A

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

A. Patient Group Information	
Name	*Filomena Servidio-Italiano*
Position	*CCRAN, President & CEO*
Date	*20/06/22*
☒	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	☐
No		
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
No.		

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	☐	☐	☐	☐

A. Patient Group Information	
Name	*Jackie Manthorne*
Position	*CCSN, President & CEO*

Date	*20/06/22*
☒	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

4. Did you receive help from outside your patient group to complete your feedback?	No	☐
	Yes	☒

Yes, CCRAN completed the feedback submission.

5. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐

No.

C. Previously Disclosed Conflict of Interest

2. 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

6. 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	☐	☐	☐	☐