Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

nivolumab ipilimumab

(non-sponsored review)

Indication: Indicated in neoadjuvant setting for resectable stage III melanoma.

Jan 3, 2025

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**PX0371-000**
Brand name (generic)	Nivolumab + Ipilimumab
Indication(s)	Indicated in neoadjuvant setting for resectable stage III melanoma.
Organization	Melanoma Canada
Contact information[a]	Name: Falyn Katz

Stakeholder agreement with the draft recommendation

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

Advanced melanoma has a high risk of relapse and mortality, especially in young individuals.

There is a need for treatments that improve survival rates while minimizing side effects and maintaining quality of life. Neoadjuvant administration of these important therapies provides an opportunity for improved response rates and prevention of disease spread. We strongly support this recommendation.

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	☐

While we are of the opinion that this usage of the combination therapy will end up being cost neutral or may actually reduce health care costs, in time, the data may support this belief. Regardless, neoadjuvant treatment has great potential to reduce spread of disease, recurrence and potentially eliminate the need for costly and debilitating surgeries. It will also aid in reducing anxiety and stress for patients in many cases, as there is reduced wait for treatment.

[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	*Falyn Katz*
Position	*CEO*
Date	*13/12/2024*
☒	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	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0371
Brand name (generic)	Ipilimumab-nivolumab
Indication(s)	neoadjuvant setting for resectable stage III melanoma
Organization	OH (CCO) Skin Cancer Drug Advisory Committee
Contact information[a]	Name: Dr. Nicole Look Hong

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.

However, for Table 2,
a) Under Discontinuation and Renewal – implementation guidance:

- Patients with BRAF mutation who experience intolerance to dabrafenib-trametinib should be able to switch to immunotherapy (nivolumab or pembrolizumab). This is the standard practice for adjuvant dabrafenib-trametinib where intolerance is encountered. The DAC does not think the prior exposure to neoadjuvant therapy should impact the drug access of patients receiving adjuvant therapy. There should be flexibility for shared decision making for the patient and physician.
- For patients who are BRAF wild-type, adjuvant pembrolizumab should be an option for partial or non-responders, instead of nivolumab, at the discretion of the treating clinician. There should be flexibility for shared decision making for the patient and physician. The use of adjuvant pembrolizumab allows for a q6weekly dosing which will save on chair time.

b) Under Cost – reason:

- Given 50% of trial patients had a major pathologic response, the Skin DAC believes that overall, the use of neoadjuvant ipilimumab-nivolumab will reduce the cost to the province.

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.

There are a lot of provisional algorithm questions that need to be addressed.

	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐
If not, please provide details regarding the information that requires clarification. See also the responses to question 1.		

[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. OH (CCO) provided a secretariat function to the group.		
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. Marcus Butler • Dr. Elaine McWhirter • Dr. Teresa Petrella • Dr. Xinni Song • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Dr. Nicole Look Hong
Position	Lead, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee lead
Date	13-Dec-2024
☒	**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**

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0371
Name of the drug and Indication(s)	Nivolumab-ipilimumab
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

Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

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

a) Recommendation rationale

Please provide details regarding the information that requires clarification.

b) Reimbursement conditions and related reasons

Please provide details regarding the information that requires clarification.

In Table 2, under Discontinuation and Renewal, PAG requested adding treatment duration and number of cycles in the adjuvant setting in patients who did not have a major pathological response.

Regarding patients who did not have a major pathological response and who have a BRAF mutation, PAG requested clarification whether adjuvant immuno-oncology treatment is an option when adjuvant dabrafenib-trametinib cannot be given.

c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. In the Drug Program Input table, under Special Implementation Issues, PAG wanted to confirm whether patients with ECOG >1 could receive this treatment at the discretion of the clinicians. The current statement from the clinical experts was based on their understanding that they needed to align with the evidence, but they agreed on the Initiation condition (Table 1) of "good performance status".

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. A panel algorithm is needed. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PX0371-000
Brand name (generic)	Nivolumab ipilimumab
Indication(s)	Indicated in neoadjuvant setting for resectable stage III melanoma.
Organization	Bristol Myers Squibb
Contact information[a]	Name: [redacted]

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

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	☐
Not applicable		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

Page 6: Clinical Value

The first bullet point describes two potentially contentious issues: 1) that EFS (Event-Free Survival) and pCR (pathological Complete Response) have not been validated against OS (Overall Survival). However, it is important to note that the primary endpoint of adjuvant studies is recurrence-free survival (RFS). Both anti-PD1 antibodies, nivolumab and pembrolizumab, as well as the combination of BRAF-targeted therapies dabrafenib and trametinib, have been approved and are currently reimbursed based on a statistically significant RFS benefit, even in the absence of a statistically significant OS benefit.

Additionally, the authors may have intended to refer to "major pathological response" (MPR) rather than "pathological complete response" (pCR), as it is the MPR that influences the decision to continue treatment into the adjuvant setting.

The authors also state that nivolumab combined with ipilimumab in this setting has not shown superiority to the standard of care neoadjuvant-adjuvant pembrolizumab. This assumption appears to be based on the phase 2 SWOG1801 study. However, pembrolizumab does not have Health Canada approval for this indication, and outside of the phase 2 SWOG1801 study, there is no additional evidence to support this statement.

It may be more appropriate to consider that a randomized phase 3 study of neoadjuvant nivolumab combined with ipilimumab, utilizing a Health Canada-approved standard of care control arm of adjuvant nivolumab, would provide a higher category of evidence in this patient population.

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	☐

The authors described a scenario where a patient does not achieve a major pathological response (MPR) with neoadjuvant nivolumab and ipilimumab, subsequently moves on to adjuvant anti-PD1 therapy, then progresses to metastatic disease and can access BRAF-targeted therapy. However, with the CDA report published in August 2024 (project number PX0347000) recommending that nivolumab and ipilimumab be reimbursed for patients who progress while on or within 6 months of their adjuvant anti-PD1 therapy, it should be noted that the same patient should be able to access the metastatic dose of nivolumab and ipilimumab.

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