Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Pembrolizumab

Reimbursement request: For the neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma
Final recommendation: Reimburse with conditions

Summary of Recommendation

The Formulary Management Expert Committee (FMEC) concluded that neoadjuvant-adjuvant pembrolizumab shows at least similar efficacy to adjuvant pembrolizumab in patients with resectable stage III or stage IV melanoma. FMEC reviewed the SWOG S1801 trial, evidence from which suggested that neoadjuvant-adjuvant pembrolizumab lengthens event-free survival compared with adjuvant pembrolizumab. FMEC acknowledged the uncertainty surrounding the magnitude of the comparative benefits, introduced by the small number of events in the analyses, the risk of assessment and reporting bias, and the absence of data to inform long-term efficacy.

FMEC also considered that neoadjuvant-adjuvant pembrolizumab meets patients' unmet needs by allowing treatment initiation promptly upon diagnosis, while patients are awaiting surgical resection.

Neoadjuvant-adjuvant pembrolizumab is expected to be cost-neutral in terms of drug costs compared to adjuvant pembrolizumab. Therefore, FMEC recommends that neoadjuvant-adjuvant pembrolizumab be reimbursed for patients with resectable stage III or stage IV melanoma if the conditions below are met. Reimbursement should be restricted to patients whose disease characteristics are consistent with those of the patients included in the SWOG S1801 trial.

Therapeutic Landscape

What Is Melanoma and How Is it Treated?

Malignant melanoma is a relatively uncommon aggressive skin cancer associated with a high risk of relapse and death. It is, however, 1 of the most common types of cancer diagnosed in younger individuals, with incidence rising over time. For patients with resectable stage III or stage IV melanoma, initial surgical resection, followed by adjuvant therapy for patients who are considered at high risk for recurrence, is the current standard of care. The goals of therapy are to extend survival, delay disease progression and/or recurrence, and improve quality of life.

Why Did We Conduct This Review?

Based on new published evidence examining neoadjuvant therapy for adult patients with resectable melanoma, publicly funded drug plans requested a Non-Sponsored Reimbursement Review and Recommendation.

Person With Lived Experience

A person with lived experience residing in rural Ontario presented his experience living with stage IIIb melanoma after a biopsy determined it spread to 2 lymph nodes in his neck. He initiated treatment with pembrolizumab, undergoing 3 treatments, 3 weeks apart before curative surgery. He explained that presurgery PET scan showed positive signs that the tumours in his lymph nodes shrunk, and that 1 was fully destroyed following treatment. During surgery, a total of 54 lymph nodes were removed successfully. His ongoing side effects were described as exhaustion, joint aches, occasional redness in the face and some weight loss; however, he continues to maintain a good quality of life and has been able to work. He now continues treatment every 6 weeks, and despite the ability to move his treatment closer to home to reduce travel times and financial burdens, he highlighted that choice in treatment access is important to patients like him, and that feeling comfortable with one's medical team has been crucial to the success of his treatment.

Input From Community Partners

What Did We Hear From Patients?

Melanoma has a profound and multifaceted impact on patients and their families, leaving them facing a wide range of physical and emotional challenges. Patients place a high value on improving their medical condition and overall quality of life. They highlight a need for access to drugs that expedite treatment initiation, mitigate risk during surgical wait times, and reduce surgical morbidity. Alleviating the negative impact of postsurgery scarring on patients' emotional and mental well-being was also highlighted as a significant concern.

What Did We Hear From Clinicians?

Clinician groups emphasized the unmet need for a curative-intent, neoadjuvant option to initiate treatment before surgery in patients with stage III or IV resectable melanoma. This is a strategy recommended by international treatment guidelines.

What Did We Hear From the Pharmaceutical Industry?

No industry input was received.

What Did We Hear From Public Drug Programs?

Public drug plans inquired about factors that can impact implementation, including optimal duration of therapy, timing of postsurgery treatment reinitiation, use of extended interval dosing, and potential criteria alignment for PD-L 1 inhibitors.

Refer to Stakeholder Input section of the clinical and pharmacoeconomic report.

Deliberation

With a unanimous vote, the FMEC concluded that neoadjuvant-adjuvant pembrolizumab shows at least similar efficacy to adjuvant pembrolizumab, identified as the most relevant comparator. Neoadjuvant-adjuvant pembrolizumab meets patients' unmet needs by allowing treatment initiation promptly upon diagnosis while awaiting surgical resection. In addition, neoadjuvant-adjuvant pembrolizumab is expected to be cost-neutral compared to adjuvant pembrolizumab.

FMEC deliberated on the following 6 domains as illustrated in the Deliberative Framework (Figure 1):

- Clinical Value: whether the drug under review provides clinical value.
- Unmet Clinical Need: whether there is an unmet clinical need that available treatment(s) is or are not currently addressing.
- Comparable Efficacy: whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.
- Patient Perspective: whether the drug under review addresses patients' specific unmet needs and values.
- Health System and Social Considerations: whether there are health system or social considerations (e.g., administration, testing, equity, access, ethical) for the drug under review.
- Economic Implications: the economic implications of reimbursing the drug under review based on public list prices.

Figure 1: Deliberative Framework

Decision Summary

Table 1: Why Did FMEC Make This Recommendation?

Domains	Reason
Patient Perspective: whether the drug under review addresses patients' specific unmet needs and values.	• Patients expressed the need for expediting treatment initiation, which in turn would mitigate risk during surgical wait times and reduce surgical morbidity, including alleviation of the negative impact of postsurgery scarring on patients' emotional and mental well-being. • FMEC acknowledged that depression and anxiety while awaiting treatment initiation are an important unmet need, which neoadjuvant-adjuvant pembrolizumab may help address. • FMEC could not assess potential treatment effects on surgical morbidity. • The input received indicated that patients and their families placed a high value on improvement in medical condition and in overall quality of life. FMEC noted that the evidence available from the SWOG S1801 trial only partially addressed these concerns.
Clinical Value: whether the drug under review provides clinical value.	• FMEC reviewed the evidence from the SWOG S1801 trial and concluded that neoadjuvant-adjuvant pembrolizumab lengthens event-free survival in patients with resectable stage III or stage IV melanoma compared with adjuvant pembrolizumab. • The SWOG S1801 trial relied on event-free survival as a surrogate for overall survival. Though event-free survival is not validated in this population, clinical experts indicated that surrogate outcomes such as event-free survival are commonly used to inform treatment decisions, as mortality has decreased substantially with advances in the treatment of melanoma. • FMEC acknowledged that there is uncertainty surrounding the findings in the SWOG S1801 trial, introduced by the small number of events in the analyses, the risk of assessment and reporting bias, and the absence of data to inform long-term efficacy (beyond 2 years). • No additional safety concerns regarding the use of pembrolizumab in the neoadjuvant-adjuvant setting compared to the current adjuvant setting were identified. • FMEC considers that the potential benefits of neoadjuvant-adjuvant pembrolizumab outweigh the uncertainty of the clinical trial's results.
Unmet Clinical Need: whether there is an unmet clinical need that available treatment(s) is or are not currently addressing.	• FMEC highlighted a significant unmet need for patients who have limited access to treatments due to potential delays in surgical procedures across Canada. Neoadjuvant pembrolizumab can be initiated promptly upon diagnosis, so that patients can access cancer treatment while waiting for initial surgical resection.
Comparable Efficacy: whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.	• FMEC highlighted that pembrolizumab is currently funded for the adjuvant treatment of patients with stage IIIA to IIID melanoma and that the main difference regarding its use in the neoadjuvant-adjuvant setting would be an earlier onset of treatment. • FMEC considered that neoadjuvant-adjuvant pembrolizumab shows at least similar efficacy to adjuvant pembrolizumab. They acknowledged that there is uncertainty surrounding the magnitude of the comparative benefits in the SWOG S1801 trial.
Health System and Social Considerations: whether there are health system or social considerations for the drug under review.	• FMEC heard that there may be significant delays in access to surgery across Canada. FMEC considered that initiating treatment promptly upon diagnosis with neoadjuvant pembrolizumab addresses this health systems issue.

Domains	Reason
Economic Implications: what are the economic implications of reimbursing the drug under review based on public list price.	• Neoadjuvant-adjuvant pembrolizumab is expected to be cost-neutral compared to adjuvant pembrolizumab.

Full Recommendation

With a unanimous vote, the FMEC recommends that pembrolizumab be reimbursed for the neoadjuvant-adjuvant treatment of adult patients with stage III or stage IV melanoma, if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Pembrolizumab should be reimbursed in the neoadjuvant-adjuvant setting in patients eligible for pembrolizumab in the adjuvant setting, i.e., with clinically detectable and measurable stage IIIB-D or resectable stage IV melanoma.	Treatment with neoadjuvant-adjuvant pembrolizumab should be reimbursed for patients whose disease characteristics are consistent with those of patients included in the SWOG S1801 clinical trial.	Pre-treatment imaging and after 3 cycles should be performed to assess response and suitability for surgery.
Discontinuation		
Pembrolizumab should be continued until a maximum of 18 doses.	The SWOG S1801 clinical trial investigated the use of pembrolizumab until a range of events related to disease progression or recurrence or toxicity occurred, up to a maximum of 18 doses.	–
Prescribing		
Pembrolizumab must be initiated by a clinician with expertise in the treatment of melanoma.	Patients with melanoma are expected to be under the care of an experienced clinical team to address the complexity of treatment, maximize potential benefits, and mitigate adverse events.	–

Feedback on Draft Recommendation

Save Your Skin Foundation, Melanoma Canada, Ontario Health Skin Cancer Drug Advisory Committee, and the Provincial Advisory Group provided feedback on the draft recommendation and agreed with the committee's recommendation. Patient and clinician partners highlighted the need for subsequent treatment after neoadjuvant pembrolizumab, which was out of scope for this review.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 1 medical oncologist from Alberta and 1 medical oncologist from Ontario. 1 expert committee member did not attend.

Meeting date: May 10, 2024

Conflicts of interest: None

Special thanks: Canada's Drug Agency extends our special thanks to the individual who presented directly to FMEC on behalf of people with lived experience, as well as the patient organizations representing the community of those living with Melanoma, notably the Save Your Skin Foundation, which include Kathleen Barnard, Jasmine MacGowan, and Dwayne and Wendy Conrad.

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