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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: Adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

Note: This document was initially published on November 22, 2022, and subsequently revised on January 31, 2023, to correct an error in the results for the budget impact analysis.

CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda should be reimbursed by public drug plans for the treatment of stage IIB/IIC melanoma following complete resection only if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients who have stage IIB or stage IIC melanoma who have not received prior treatment beyond surgery.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed in an outpatient oncology clinic and supervised by a specialist who has experience in delivery of immunotherapy, and if the cost of Keytruda is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from 1 clinical trial demonstrated that more patients treated with Keytruda did not have their melanoma return and did not have their cancer spread, compared to patients that received placebo.
- Patients identified a need for treatments that reduce the risk of their melanoma returning and are not associated with unmanageable side effects. Based on 1 clinical trial, Keytruda may address these needs.
- Based on CADTH's assessment of the health economic evidence, Keytruda does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Keytruda is estimated to cost the public drug plans approximately $85,970,178 million over the next 3 years.

Additional Information

What Is Stage IIB or Stage IIC Melanoma?

Stage IIB or IIC melanoma is a kind of skin cancer that occurs in skin cells that produce melanin. The Canadian Cancer Society has estimated that in 2022, 9,000 Canadians will be diagnosed with melanoma skin cancer and 1,200 people will die from it.

Unmet Needs in Stage IIB or Stage IIC Melanoma

Surgery for stage IIB or IIC melanoma is intended to cure patients. However, in some cases, patients have a poor prognosis and are at risk for their skin cancer returning. Therefore, there is a need for treatment options that can help prevent melanoma from coming back.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per patient per 28-day cycle.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, multi-centre, placebo-controlled study (KEYNOTE-716) demonstrated that adjuvant treatment with pembrolizumab resulted in added clinical benefit for patients with resected stage IIB or IIC cutaneous melanoma. The KEYNOTE-716 study demonstrated that administration of pembrolizumab every 3 weeks for up to 1 year of treatment (or 17 cycles) was associated with statistically significant and clinically meaningful improvements in recurrence-free survival (RFS) compared to placebo. This was based on the primary analysis of RFS at interim analysis 1 (IA1) (hazard ratio [HR] = 0.65; 95% CI, 0.46 to 0.92; P = 0.00658), which was consistent with the results of the final analysis of RFS at IA2 (HR = 0.61; 95% CI, 0.45 to 0.82; nominal P = [redacted]), at 18 months of follow-up. Distant metastasis-free survival (DMFS) was a key secondary end point in the KEYNOTE-716 study and was also in favour of pembrolizumab at 18 months (HR = 0.64; 95% CI, 0.47 to 0.88; P = 0.00292). Although exploratory, treatment with pembrolizumab was not associated with a detriment in health-related quality of life (HRQoL). Pembrolizumab was associated with a manageable toxicity profile.

pERC acknowledged the need for a treatment for patients with stage IIB or IIC cutaneous melanoma, as this population generally has a poor prognosis and high risk of disease recurrence. Patients identified a need for access to effective treatments that reduce the risk of disease recurrence and improve quality of life, particularly by reducing the severity of side effects associated with treatment. Given the totality of the evidence, pERC concluded that pembrolizumab met some of the needs identified by patients in terms of reducing the risk of disease recurrence and providing a manageable toxicity profile.

The cost-effectiveness of pembrolizumab is highly uncertain due to the absence of overall survival data in a format CADTH can assess and extrapolate, and the lack of face validity of the sponsor's extrapolated overall survival curves. CADTH could not derive a base-case analysis due to serious uncertainty, and therefore, an exploratory analysis was conducted which considered the cost-effectiveness of pembrolizumab relative to observation. Based on the sponsor's submitted price for pembrolizumab and publicly listed prices for all other drug costs, the estimated incremental cost-effectiveness ratio (ICER) was $110,594 per quality-adjusted life-year (QALY) gained, compared with observation. At that ICER, a price reduction would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained. The committee indicated that greater price reductions may be required due to the uncertainty around the exploratory reanalysis.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients who have stage IIB or stage IIC melanoma (as defined by the American Joint Committee on Cancer 2017 classification, eighth edition)	In the KEYNOTE-716 study, treatment with pembrolizumab demonstrated a clinically meaningful benefit in patients with these characteristics.	—
2. Treatment with pembrolizumab should be initiated within 12 weeks of surgery	The benefit of treatment with pembrolizumab has not been demonstrated in patients treated more than 12 weeks after surgery. This is also consistent with adjuvant treatment in clinical practice.	—
3. Patient must not have received prior treatment beyond complete resection	Patients enrolled in the KEYNOTE-716 study did not have prior systemic therapy for stage II melanoma. As such, the potential benefit of pembrolizumab in these patients has not been demonstrated.	—
Discontinuation		
4. Reimbursement of pembrolizumab should be discontinued in patients who exhibit any of the following: 4.1. clinical or radiological disease progression 4.2. evidence of significant toxicity or adverse events potentially related to pembrolizumab	As per the results available for the KEYNOTE-716 study, the benefit of pembrolizumab following disease progression has not yet been demonstrated. Discontinuation due to toxicity or adverse events is consistent with clinical practice.	—
5. Patients should discontinue treatment following a maximum of 17 cycles of adjuvant pembrolizumab	As per KEYNOTE-716 criteria, in which patients were treated with pembrolizumab 200 mg administered intravenously every 3 weeks for a maximum of 17 cycles (or 1 year).	—
Prescribing		
6. Pembrolizumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in delivery of immunotherapy	To ensure that pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
7. Pembrolizumab should not be used in combination with other anticancer drugs.	No evidence supporting the efficacy and safety of pembrolizumab in combination with other anticancer drugs for this indication was identified.	—
Pricing		
8. A reduction in price	The cost-effectiveness of pembrolizumab is highly uncertain. CADTH undertook an exploratory reanalysis, which indicated that at least a 40.7% reduction in price is required to achieve an ICER of $50,000 per QALY.	—

Reimbursement condition	Reason	Implementation guidance
Feasibility of adoption		
9. The feasibility of adoption of pembrolizumab must be addressed	At the submitted price, the budget impact of pembrolizumab is expected to be greater than $40 million in year 3.	—

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- pERC deliberated on the acceptability of RFS as an acceptable surrogate for overall survival (OS). Overall, pERC concluded that RFS as a surrogate for OS is uncertain, but that RFS was a meaningful outcome to patients with melanoma. Further, pERC concluded that the improvement in RFS observed in the KEYNOTE-716 study was clinically meaningful.
- pERC noted that the impact of pembrolizumab treatment on OS remains uncertain, as data from the KEYNOTE-716 study were immature at the time of review.
- pERC discussed that while a significant detriment to HRQoL was not observed in patients treated with pembrolizumab in the KEYNOTE-716 study, a small minority of patients may suffer immune-mediated side effects with potentially lifelong consequences. Although rare, long-term immune-related toxicities can be severe, and the risks associated with treatment should be discussed with patients. Of note, the toxicity profile for pembrolizumab is established and physicians are familiar with mitigating adverse events.
- pERC noted that there is uncertainty regarding the efficacy of downstream immunotherapy following adjuvant treatment of pembrolizumab.

Background

Melanoma is a cancer that begins in the melanocyte cells of the skin, also referred to as cutaneous melanoma. Cutaneous melanomas can develop anywhere on the skin, including the eyes, mouth, genitals, and anal area; however, they are most likely to start on the chest, back, and legs. In contrast, non-cutaneous melanoma develops from skin cells other than melanocytes, such as basal cells. The first signs of melanoma skin cancer are typically a change in the mole colour, size, or shape. Other common signs and symptoms include a mole that is asymmetric, has an uneven or irregular border, is not the same colour throughout, is large in diameter (more than 6 mm), or is evolving. The cancerous growth has the potential to grow into and destroy nearby tissue or metastasize to other parts of the body. The Canadian Cancer Society has estimated that in 2022, 9,000 Canadians will be diagnosed with melanoma skin cancer and 1,200 people will die from it. The Canadian Cancer Society also reported that melanoma accounts for about 3.8% and 3.3% of new cancer cases in men and in women, respectively. Further, melanoma accounts for 1.9% and 1.2% of all cancer deaths in men and in women, respectively. Risk factors for melanoma skin cancer include: UV radiation; many moles; atypical moles; congenital melanocytic nevi; familial atypical multiple mole melanoma syndrome; other hereditary conditions (xeroderma pigmentosum, Werner syndrome, retinoblastoma); light-coloured skin, eyes, and hair; personal or family history of skin cancer; CDKN2A gene mutation; and a weakened immune system.

A diagnosis of melanoma usually begins with a family physician, based on reported signs or symptoms and a skin exam. Patients may then be referred to a specialist, such as a dermatologist or surgeon, as needed. The presence of cancerous cells, and extent and characteristics of disease, may be identified by performing a skin biopsy or lymph node biopsy, or through histology, imaging (CT scan, MRI, chest X-ray, PET scan), or blood tests. Patients with stage IIB and IIC melanoma are defined by having high-risk node-negative disease. The primary tumour is thick and/or ulcerated (greater than 4 mm thick with or without ulceration, or greater than 2 to 4 mm thick with ulceration), but there is no lymph node involvement.

According to the clinical experts consulted by CADTH, following a diagnostic biopsy, all patients should undergo wide-local excision (WLE) of the primary site, which is a curative-intent surgical procedure. Following definitive WLE, the standard of care is to follow patients for surveillance. As per the 2020 Canadian Melanoma Conference recommendations, surveillance should be conducted by an appropriate specialist, including biannual visits and PET/CT with brain MRI among the systemic imaging modalities available. The Canadian Melanoma Conference recommendation statement also indicated that high-risk surveillance should follow a 5-year schedule, beginning with an intensive 2-year period, followed by a less-intensive 3-year period, as the median time to relapse for stage IIB to III melanoma is less than 2 years after treatment.

Pembrolizumab is an immune checkpoint inhibitor (ICI) that binds to programmed cell death receptor-1 (PD-1), resulting in the reactivation of tumour-specific cytotoxic T lymphocytes in the tumour microenvironment. Pembrolizumab is indicated for the adjuvant treatment of adult and pediatric patients (aged 12 years and older) with stage IIB or IIC melanoma following complete resection. The sponsor has requested that pembrolizumab be reimbursed as per the indication. The Notice of Compliance (NOC) was received on July 5, 2022. In December 2021, the FDA approved pembrolizumab for the adjuvant treatment of adult and pediatric patients (aged 12 years and older) with stage IIB, IIC, or III melanoma following complete resection. Pembrolizumab was previously reviewed by CADTH for the adjuvant treatment of patients with stage IIIA to stage IIID cutaneous melanoma and received a recommendation for reimbursement with conditions.

Pembrolizumab has been approved by Health Canada for adjuvant treatment of adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection. Pembrolizumab is an immunoglobulin G4 (IgG4) monoclonal antibody against programmed cell death protein 1 (PD-1). Pembrolizumab is administered as an IV infusion over 30 minutes. For adults, the recommended dosage for adjuvant treatment of melanoma is either 200 mg every 3 weeks or 400 mg every 6 weeks, for up to 1 year or until disease recurrence or unacceptable toxicity. For pediatric patients, recommended dosage for adjuvant treatment of melanoma is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks, until disease progression or unacceptable toxicity, or for a maximum of 12 months.

Sources of Information Used by the Committee

To make their recommendation, the committee considered the following information:

- a review of 1 randomized controlled trial in patients at least 12 years of age with resected stage IIB or IIC cutaneous melanoma
- patients' perspectives gathered by 2 patient groups, the Save Your Skin Foundation (SYSF) and Melanoma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- two clinical specialists with expertise in diagnosing and treating patients with stage IIB or IIC cutaneous melanoma
- input from 1 clinician group, the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, SYSF and Melanoma Canada, submitted patient input for this review. Both groups included patients from across Canada with melanoma, regardless of cancer stage. SYSF gathered data through online surveys, virtual roundtables, and one-on-one discussions with 25 melanoma patients (68% female), 18 of which received the treatment under review. Melanoma Canada received input from 172 melanoma patients (67% female) and 15 caretakers through an online survey. Twenty patients from the Melanoma Canada submission indicated that they had been on treatment with adjuvant pembrolizumab for stage IIB or IIC melanoma following complete resection.

According to the SYSF input, respondents who were diagnosed with stage II melanoma reported having limited access to available treatment options, which increased their initial fear and anxiety. The Melanoma Canada survey respondents indicated that the main day-to-day impacts of their diagnosis included scarring and disfigurement, fear or anxiety, and disrupted sleep, as well as pain, fatigue, and depression. Respondents also indicated mobility and lymphedema issues caused by surgery including lymph node dissection. The input suggested that there is an unmet need for treatment options to prevent recurrence of disease, as there are currently no treatment options available beyond surgery for stage IIB or IIC disease in Canada.

In both submissions, most patients who had experience with the treatment under review reported experiencing at least 1 side effect. In the SYSF submission, the main side effects reported by the survey respondents included fatigue, cognitive impairment, nausea, skin rash, gastrointestinal problems, and weight loss or gain. Most patients found these side effects to be manageable. In the Melanoma Canada submission, the main reported side effects included fatigue or weakness, skin rash, thyroid or pituitary gland issues, and muscle or joint pain. Most of the respondents indicated that they were willing to accept the side effect profile of pembrolizumab if it would potentially mean that they would not have to

deal with a recurrence. A common concern among patients was the length of time and cost of travel to get to a clinical trial site for treatment. According to the submissions received, patients expressed a need for future treatments that would be curative; be accessed close to home and delivered in a timely fashion; allow them to work and continue normal day-to-day activities without significant long-term side effects; and be available to them if their disease was to progress or recur.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of stage IIB or IIC melanoma who were consulted by CADTH on this review.

The clinical experts described the prognosis of stage IIB or IIC patients as similar to that observed in Stage III (lymph node positive) malignant melanoma. The clinical experts stated that the standard of care for patients with resected Stage III melanoma involves systemic treatment as adjuvant treatment after surgery. In contrast, the experts noted that there are no currently available systemic therapies other than high-dose interferon, which is rarely used, for adjuvant treatment to surgery for patients with resected stage IIB or IIC melanoma. Given the similarities between the prognoses of patients with stage IIB or IIC and III melanoma diagnoses, the experts indicated that patients and clinicians would likely want access to systemic treatment for similar adjuvant treatment of these patients.

The clinical experts indicated that pembrolizumab would be the first available systemic therapy for adjuvant use in resected stage IIB or IIC melanoma, although clinical trials investigating the efficacy and safety of nivolumab and encorafenib plus binimetinib are ongoing. According to the clinical experts, one would expect that pembrolizumab would be used as monotherapy, with a small minority of patients within this category qualifying for consideration of radiation therapy as adjuvant treatment to surgery. The clinical experts felt that approval of pembrolizumab for adjuvant treatment to surgery for patients with resected stage II melanoma would shift the current treatment paradigm. The clinical experts indicated that for reference, in their experience, the incidence of stage II melanoma diagnoses is roughly twice that of stage III, suggesting a significant increase in the number of melanoma patients eligible for treatment with adjuvant immunotherapy. However, that number may overestimate the impact of introducing pembrolizumab to the stage II patient population, as presumably a proportion of patients would recur with nodal disease (at which point they may be candidates for treatment with adjuvant systemic therapy).

The clinical experts explained that currently, there are no biomarkers in regular clinical use that would guide treatment decision-making in melanoma. The clinical experts felt that patients with stage IIB and IIC melanoma will likely be considered equally for treatment with pembrolizumab as adjuvant treatment to surgery, in alignment with the criteria used in the KEYNOTE-716 study. According to the experts, patient-specific factors, including performance status, the presence or absence of relevant comorbidities, patient age, and patient wishes will guide decisions about treatment with pembrolizumab for patients with resected stage IIB or IIC melanoma. They also noted that patients with active autoimmune medical comorbidities (i.e., inflammatory bowel disease, rheumatoid arthritis), would not be exempt from treatment, but may be less likely to pursue treatment with adjuvant immunotherapy.

The clinical experts acknowledged that although an improvement in OS is the primary outcome of interest, an improvement in RFS is still of clinical value. They further described

response to treatment, defined by the absence of disease, as a clinically meaningful outcome that is consistent with outcomes used for other adjuvant indications. According to the clinical experts, most clinicians will re-stage patients to ensure against disease relapse during adjuvant therapy. They further noted that practices are likely to vary between jurisdictions, and it is unlikely that most patients and clinicians will adhere to a schedule as robust as that used in the KEYNOTE-716 trial.

With regard to discontinuation of treatment, the experts indicated that patients should be monitored for treatment-related toxicities during pembrolizumab therapy, and treatment may be discontinued if moderate or severe toxicities occur. The clinical experts referenced the recommendations from the European Society for Medical Oncology[9] and the American Society for Clinical Oncology[10] as generally accepted algorithms that exist for managing immune-related toxicities. The experts felt that whether or not adjuvant therapy should be automatically discontinued in the setting of disease recurrence is debatable and should be decided on a case-by-case basis. The clinical experts recommended that treatment with pembrolizumab as an adjuvant treatment to surgery be overseen by a qualified medical oncologist, with support from community cancer centres and allied health care providers.

Clinician Group Input

Clinician group input was received from the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee, with 5 clinicians contributing to the submission. The clinician group noted that there is currently no treatment for this high-risk patient population, and currently sentinel node-negative patients are ineligible for adjuvant treatment, indicating an unmet need. The treatment goal for this patient population would be RFS, as it is an important end point for patients while being a possible surrogate for OS. The input stated that pembrolizumab would be provided as an adjuvant treatment after appropriate surgical management. The input suggests that treatment should be provided in an outpatient setting; physical exams and CT scans should be used to determine if a patient is responding to treatment; and treatment should be discontinued upon disease recurrence and toxicity.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for pembrolizumab:

- relevant comparators
- considerations for initiation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The KEYNOTE-716 trial used a placebo comparator. There are no standard funded therapies in Canada for this indication.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
In the KEYNOTE-716 study, patients in the placebo arm who experienced recurrence, and patients in the pembrolizumab arm who experienced recurrence more than 6 months after completing 17 cycles of treatment, were eligible to cross over or rechallenge with pembrolizumab for up to 2 years. PAG highlighted that in other solid tumours (e.g., lung, melanoma), patients are eligible for downstream PD-1 or PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of an adjuvant PD-1 or PD-L1 inhibitor. Can the same principle be applied in this setting?	The clinical experts indicated that the same principle used for other solid tumours could be applied to the treatment setting for patients with stage II melanoma. Overall, the experts felt that stage II melanoma should not be treated any differently from stage III. pERC agreed with the clinical experts, noting the same principles used for other recommendations should be applied.
Considerations for prescribing of therapy	
Pembrolizumab dosing on KEYNOTE- 716 (the phase 3 trial of Stage IIB/C melanoma) was 200 mg (2 mg/kg for pediatrics) IV q21days x 17 doses. If funded, in line with other indications for pembrolizumab, jurisdictions would implement a weight-based dose of 2 mg/kg (up to a cap of 200 mg) for all patients. Other indications for pembrolizumab use extended dosing intervals of q6weekly (4mg/kg up to a 400 mg cap). Is a dosing interval of every 6 weeks of pembrolizumab appropriate for Stage IIB/C melanoma?	The clinical experts felt that a dosing interval of every 6 weeks would be appropriate for most patients. They shared that clinicians may wish to initiate treatment on a 21-day schedule, but for the majority of patients, a 42-day schedule will be acceptable (and for many patients, likely preferred). However, they also noted that the KEYNOTE-716 clinical trial used a 21-day schedule, and extrapolation of that data to a 42-day schedule is not automatic. pERC agreed with the clinical experts.
Generalizability	
Should patients with an ECOG performance status of 2 or greater be eligible for pembrolizumab in this indication?	The clinical experts indicated that patients with an ECOG performance status of 2 or greater should be eligible for pembrolizumab. They stated that it is important to note that within the adjuvant patient population, diminished performance status is not disease-related, as patients have been rendered surgically free of disease before treatment. Clinicians and patients will likely be willing to treat patients with an ECOG performance status of 2 with pembrolizumab, given the manageable tolerability profile. pERC agreed with the clinical experts, noting that patients with an ECOG score of 2 would be very rare in the adjuvant population.
Should patients with non-cutaneous melanoma be considered for treatment with pembrolizumab for this indication? Current pembrolizumab indication in stage III adjuvant melanoma allows treatment for mucosal melanoma and excludes ocular or uveal melanoma.	The clinical experts felt it would be reasonable to use the same patient selection criteria for non-cutaneous stage II as what is used for stage III. pERC agreed with the clinical experts.

Implementation issues	Response
Care provision issues	
Pembrolizumab is already prepared and administered at facilities throughout Canada. Health care professionals have extensive experience with it. Preparation and administration time for pembrolizumab are relatively reasonable and would not be expected to create a significant increase to health system resources.	Comment from the drug programs to inform pERC deliberations.

ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The pivotal trial for pembrolizumab (KEYNOTE-716) was the only study included in the CADTH systematic review. The KEYNOTE-716 study (N = 976) was a randomized, placebo-controlled, parallel-group, crossover/rechallenge, multi-centre study of adjuvant pembrolizumab in patients 12 years of age and older with resected stage IIB or IIC cutaneous melanoma. The study consisted of 2 parts: adjuvant treatment in part 1 and crossover/rechallenge after first recurrence in part 2. In part 1, pembrolizumab or placebo was administered every 3 weeks for 17 cycles. The results from part 2 were not available at the time of this review. At the time of this review, data up to interim analysis (IA) 3 was available. The data cut-off (DCO) for interim analyses were: IA1, December 4, 2020; IA2, June 21, 2021; and IA3, January 4, 2022.

The primary objective of the KEYNOTE-716 study was to compare RFS between the treatment groups, pembrolizumab and placebo. Patients included in the trial must have been enrolled within 12 weeks of final surgical resection with complete surgical wound healing and have no evidence of metastatic disease on imaging. The mean age of included patients was 59.3 years (standard deviation [SD] = 12.9) and 2 pediatric patients were included (1 randomized to each treatment group). Almost all included patients did not exhibit functional impairment (Eastern Cooperative Oncology Group [ECOG] performance status of 0 or Karnofsky Performance Scale [KPS] status of 100), and the remaining patients (7% in each treatment group) exhibited some functional impairment (ECOG performance status of 1). Most patients had stage IIB melanoma at baseline (64%) and 35% had stage IIC melanoma. In addition to RFS, data were available for the following outcomes as of IA3: DMFS, and HRQoL measured using the EORTC QLQ-C30 and the EQ-5D-5L visual analogue scale (VAS).

Efficacy Results

OS was identified as the most important outcome for patients with melanoma. At the time of this review, the available evidence did not include an assessment of OS due to data immaturity and was limited to RFS, an interim analysis of DMFS, and an exploratory analysis of HRQoL. The final OS analysis for the study is not expected to occur until approximately 180 months (15 years) of follow-up. Key efficacy results from the KEYNOTE-716 study are described below.

The final analysis of RFS was based on the June 21, 2021 DCO (IA2). Recurrence was defined as recurrence of melanoma at any site (local, in-transit, or regional lymph nodes, or distant recurrence) or death due to any cause. The median duration of follow-up for all participants (intention-to-treat population) was 20.5 months (range, 4.6 months to 32.7 months) as of the DCO, with a similar median duration of follow-up across treatment groups. The estimated HR suggested a reduction in risk of recurrence at 18 months follow-up, based on an HR of 0.61 (95% CI, 0.45 to 0.82; nominal P = [redacted]). At that time point, 72 patients (14.8%) randomized to pembrolizumab and 115 patients (23.5%) randomized to placebo had experienced recurrence of disease. The HR for RFS at IA2 was consistent with the results of the primary analysis of RFS at IA1 (HR = 0.65; 95% CI, 0.46 to 0.92; P = 0.00658) and subsequent analysis at IA3 (HR = 0.64; 95% CI, 0.50 to 0.84). In the pembrolizumab treatment group, 7.8% of events were local/regional/locoregional recurrence, 6.4% were distant recurrence, and 0.62% were deaths. In the placebo treatment group, 10.2% were local/regional/locoregional recurrence, 12.3% were distant recurrence, and 1.0% were deaths. The 2 sensitivity analyses of RFS accounted for new primary melanomas included in the RFS analysis and different censoring rules; both were consistent with the primary analysis.

The first interim analysis of DMFS was available for this review. Neither patient nor clinician groups highlighted DMFS as an outcome of particular interest compared to RFS and OS. As of IA3, the median duration of follow-up for all patients was 26.9 months (range, 4.6 months to 39.2 months). At IA3, 13% and 19% of patients randomized to pembrolizumab and placebo, respectively, experienced DMFS. The reduction in risk of DMFS at 18 months was in favour of pembrolizumab (HR = 0.64; 95% CI, 0.47 to 0.88; P = 0.00292); however, this was based on a small number of events and immature data.

The analysis of HRQoL outcomes was exploratory, but suggested little to no change in HRQoL in the placebo treatment group, and a small numerical reduction in HRQoL in the pembrolizumab treatment group. The results were reported as a change from baseline to week 48 and week 72. At week 72, the LS mean of the change from baseline in the EORTC QLQ-C30 Global Health Status/QoL scale was [redacted] (95% CI, [redacted] to [redacted]) for patients randomized to pembrolizumab and [redacted] (95% CI, [redacted] to [redacted]) for patients randomized to placebo. The LS mean change from baseline to week 72 for the EQ-5D-5L VAS was [redacted] (95% CI, [redacted] to [redacted]) for patients randomized to pembrolizumab and [redacted] (95% CI, [redacted] to [redacted]) for patients randomized to placebo.

Harms Results

Safety results reported herein were based on the January 4, 2022 DCO. A total of | deaths were reported, | of which were patients randomized to placebo. The frequency of adverse events (AEs) and serious adverse events (SAEs) reported by patients was similar between treatment groups; 95.7% and 91.6% of patients in the pembrolizumab and placebo treatment groups, respectively, reported at least 1 AE. Diarrhea ([redacted] for pembrolizumab versus placebo, respectively), pruritus ([redacted]), arthralgia ([redacted]), rash ([redacted]), headache ([redacted]), hypothyroidism ([redacted]), alanine aminotransferase increase ([redacted]), and hyperthyroidism ([redacted]) were reported more frequently by patients in the pembrolizumab treatment group than placebo. Serious AEs were reported by [redacted] of patients in the pembrolizumab treatment group and [redacted] of patients in the placebo treatment group. The most frequently reported SAEs were basal cell carcinoma ([redacted] in the pembrolizumab and placebo treatment groups, respectively), squamous cell carcinoma of the skin ([redacted]), malignant melanoma in situ ([redacted]), and malignant melanoma ([redacted]). Neither of the pediatric patients in the study reported a SAE. Numerically, more patients discontinued from treatment due to AEs in the pembrolizumab treatment group ([redacted] of patients) compared with placebo ([redacted] of patients);

however, discontinuation from treatment did not appear to be the result of any specific AEs. The clinical experts consulted by CADTH stated that patients with stage IIB or IIC melanoma following complete resection are overall considered healthy patients. They posed that as a result, some patients may not be willing to tolerate the AEs associated with pembrolizumab (for which they were involved in a trial, therefore with unknown benefit) while they felt healthy otherwise.

Notable AEs (i.e., the AEs of special interest for this review), including immune-mediated reactions (colitis and pneumonitis), severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis), infusion-related reactions, and endocrine-related reactions were observed in less than [redacted] of patients in any treatment group, with the exception of hyperthyroidism and hypothyroidism, as previously described.

Critical Appraisal

The KEYNOTE-716 study was a well-designed, randomized, placebo-controlled, parallel-group, multi-centre study. Part 1 of the study, which is the focus of this review, was double-blind. At the time of this review, data from IA3 (January 4, 2022 DCO) was the most recent analysis available. At IA3, the final analysis of RFS and the interim analysis of DMFS were the only analyses of the primary and key secondary end points that were available. Overall survival was identified as the most important outcome for the review of pembrolizumab for stage IIB or IIC melanoma; however, the final OS analysis for the study is not expected to occur until approximately 180 months (15 years) after the first patient was randomized. There was evidence based on interferon-based therapies to support RFS as a surrogate outcome for an HR of at least 0.77; however, another study concluded that more evidence is needed to confirm the strength of association between RFS and OS for immunotherapies such as pembrolizumab. Based on the evidence that is currently available, RFS may be an appropriate surrogate outcome for OS, but this is associated with notable uncertainty given the limited data available in terms of the therapies that are the current standard of care, the small number of events available for analysis, and the relatively short duration of follow-up at this time. Patient-reported HRQoL outcomes (EORTC QLQ-C30 and EQ-5D-5L VAS) were exploratory, subject to potential bias due to missing data, and not controlled for multiplicity. As such, limited conclusions can be drawn about HRQoL. Subgroup analyses were not pre-specified and not powered to show efficacy, and therefore should be considered exploratory.

Although the sponsor is requesting reimbursement of pembrolizumab for patients at least 12 years of age, only 2 pediatric patients (aged 12 to 17 years) were included in the study; therefore, the appropriateness of generalizing the results to pediatric populations is unknown. At the time of this review, the evidence was limited to Part 1 of the study, which only included patients who were not previously treated for melanoma beyond complete surgical resection. Additionally, some of the exclusion criteria in the trial — such as patients who had received prior therapy with anti-PD1, anti-programmed death-ligand 1 (anti-PD-L1), or anti-programmed death-ligand 2 (anti-PD-L2) agents; patients with a known additional malignancy or who had required active antineoplastic therapy or surgery in the past 5 years; and patients with immunodeficiencies — are likely to miss a subset of patients that would be seen in clinical practice (an estimated 5% to 10% of patients). The clinical experts indicated that these criteria would not preclude patients from treatment with pembrolizumab in practice, but the safety and efficacy of treatment in these patients is associated with uncertainty. Concomitant medication use described in the trial was considered appropriate and consistent with clinical practice. The evidence is limited to a placebo-controlled trial; however, given that the current standard of care is surveillance, this was considered to be a reasonable comparator. At

the time of this review, the final analysis was only available for the primary end point, RFS. The clinical experts indicated that approximately one-third of patients who do experience recurrence of disease will recur in the first 12 months following resection. Despite having enough events to perform the final analysis of RFS, the small number of events available for analysis may have rendered the effect estimates and corresponding confidence intervals fragile. The duration of follow-up as of IA2 and IA3 is likely too short, causing uncertainty around the generalizability of the estimate for recurrence to what would be expected in clinical practice. In contrast, the clinical experts felt that the duration of follow-up was sufficient to observe AEs of interest.

Indirect Comparisons

A focused literature search for indirect treatment comparisons (ITCs) dealing with melanoma was run in MEDLINE All (1946–) on May 20, 2022. No search limits were applied. No ITCs were identified for this review.

Other Relevant Evidence

A sponsor-submitted ITC was used to support the economic model. This ITC compared interventions of interest on the outcomes of progression-free survival (PFS) and OS in patients with unresectable stage III or IV melanoma receiving first-line treatment for advanced disease. In the BRAF all-comers/wild type population, the network meta-analysis (NMA) showed that pembrolizumab may be favourable for PFS relative to ipilimumab monotherapy, dacarbazine, ipilimumab plus dacarbazine, and binimetinib, but nivolumab plus ipilimumab was favoured relative to pembrolizumab for PFS analysis. For the OS analysis in the BRAF all-comers/wild type population, the NMA showed that pembrolizumab may be favourable relative to ipilimumab and to dacarbazine. In the population with BRAF mutation positive melanoma, pembrolizumab may be favourable for PFS relative to ipilimumab monotherapy, dacarbazine, ipilimumab plus dacarbazine, and binimetinib, but may be less favoured than nivolumab plus ipilimumab, encorafenib plus binimetinib, vemurafenib plus cobimetinib, atezolizumab plus vemurafenib and cobimetinib, dabrafenib plus trametinib, and pembrolizumab plus dabrafenib and trametinib. For the OS analysis in the population with BRAF mutation positive melanoma, pembrolizumab may be favourable to monotherapy with ipilimumab, dacarbazine, or vemurafenib.

Limitations to this NMA include variation in patient characteristics (BRAF status, PD-L1, M1c metastases, baseline characteristics such as lactate dehydrogenase [LDH] above normal and ECOG status) and trial characteristics (e.g., open label and phase II versus phase III trial), which indicate that the underlying assumption of transitivity is likely to have been violated. Potential heterogeneity was not further investigated, for example with subgroup analyses or meta-regression. Consistency between direct and indirect evidence could not be verified due to the lack of closed loops. All of the contributing evidence was indirect, which reduces the certainty of all effects. Additionally, there was limited data available for the NMAs that were conducted for OS and PFS; therefore, fixed effects models were used for these end points, which is likely to have resulted in estimates that are more precise than in reality. These limitations preclude making conclusions about the comparative effectiveness of pembrolizumab in the setting of advanced melanoma.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult and pediatric (12 years and older) patients with stage IIB or IIC melanoma following complete resection
Treatment	Pembrolizumab
Dose regimen	Adult: 200 mg every 3 weeks or 400 mg every 6 weeks until unacceptable toxicity, disease progression, or for up to 12 months Pediatric: 2 mg/kg (up to a maximum of 200 mg) every 3 weeks until unacceptable toxicity, disease progression, or for up to 12 months
Submitted price	Pembrolizumab, 100 mg, solution: $4,400.00 per 100mg/4 mL vial
Treatment cost	$11,733 per 28 days
Comparator	Observation
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data source	KEYNOTE-716 trial
Key limitations	• Neither the median recurrence-free survival (RFS) nor the median overall survival (OS) were reached by the trial data cut-off (June 21, 2021) despite having enough events to perform the final analysis of RFS at IA2. Further, OS data from the trial did not inform the economic model; rather, the sponsor submitted a model using RFS estimates as an intermediate outcome to exclusively predict the OS estimates over a lifetime time horizon. There is a lack of face validity with the model's OS curves when compared to published literature; specifically, the model predicted that 99.6% of the incremental OS benefit with pembrolizumab would be accrued after the trial period. Therefore, there is substantial uncertainty around any magnitude of modelled OS benefit. • The sponsor assumed the benefit (i.e., RFS and OS) would be sustained indefinitely after 1 year of treatment with pembrolizumab. According to clinical experts consulted by CADTH for this review and the sponsor's analysis of the RFS's Kaplan-Meier curves, the long-term impact (i.e., post 1 year) of adjuvant pembrolizumab for stage IIB and IIC melanoma on RFS or OS is uncertain. • The submitted market shares of subsequent treatments in the locoregional recurrence and distant metastasis states did not reflect Canadian clinical practice, and thus underestimated the cost of subsequent therapy in the pembrolizumab arm. • The submitted model assumed pembrolizumab would have the same effectiveness when used in subsequent lines of treatment for patients who received pembrolizumab in earlier treatment lines and in patients who were pembrolizumab-naive. However, the effectiveness of pembrolizumab when used in multiple lines of therapy is uncertain, as evidence suggests reduced effectiveness when patients are rechallenged with the same drug in comparison with patients that are receiving pembrolizumab for the first time. • The sponsor applied relative dose intensity (RDI) in the derivation of the costs for pembrolizumab and subsequent therapies. This is inappropriate, as RDI can be influenced by many different factors, and favour pembrolizumab.

Component	Description
CADTH reanalysis results	• Due to uncertainties in the OS data, CADTH could not determine a base-case cost-effectiveness estimate of pembrolizumab in the adjuvant treatment of stage IIB or IIC cutaneous melanoma. • CADTH conducted an exploratory analysis that accounted for some of the identified limitations, including incorporating waning of treatment, revising market shares for subsequent treatments, and assuming 100% RDI. CADTH was not able to address the substantial uncertainty associated with the predicted OS benefit as well as concerns regarding potential reduction in effectiveness of pembrolizumab in patients who were rechallenged with pembrolizumab at relapse. • In the CADTH exploratory reanalysis, for the proposed Health Canada indicated population, pembrolizumab was associated with an ICER of $110,594 compared to observation (incremental costs = $106,327; incremental QALYs = 0.96). For pembrolizumab to be cost-effective compared to observation at a willingness-to-pay threshold of $50,000 per QALY, a price reduction of at least 40.7% is required. The results of these reanalyses should be viewed only as exploratory, given the extensive uncertainty associated with the comparative clinical effectiveness; therefore, a higher price reduction may be warranted.

Budget Impact

CADTH identified the following key limitations: the referral rate to oncologists may be underestimated, market shares of subsequent treatments for patients who developed locoregional or distant recurrence do not reflect Canadian clinical practice, the assumption regarding patient enrolment in clinical trials as a comparator is inappropriate, and the relative dose intensity (RDI) and budget impact of patients diagnosed in years 1 to 3 were not fully captured.

CADTH's base-case revisions included: revising the proportion of patients who were assumed to be in clinical trials to 0%, increasing the referral rate to oncologists, changing subsequent treatment market shares, and setting RDI to 100%. CADTH also explored uncertainty in the price reduction, use of a weight-based pembrolizumab dose, and the incident case distribution throughout the year.

Based on CADTH's base case, the expected budget impact for funding pembrolizumab for the adjuvant treatment of adult and pediatric patients (aged 12 years and older) with stage IIB or IIC melanoma following complete resection is expected to be $8,708,492 in Year 1, $36,209,278 in Year 2, and $41,052,409 in Year 3, with a 3-year budget impact of $85,970,178.

Results of CADTH's scenario analyses demonstrate that the estimated budget impact is sensitive to the change in weight-based dosing and the timing of when individuals were diagnosed in the model.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: September 14, 2022

Regrets: 1 expert committee member did not attend.

Conflicts of interest: None