



## CADTH Reimbursement Recommendation

# Nivolumab (Opdivo)

**Indication:** As monotherapy, for the adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection

**Sponsor:** Bristol Myers Squibb

**Final recommendation:** Reimburse with conditions



# Summary

## What Is the Reimbursement Recommendation for Opdivo?

CADTH recommends that Opdivo should be reimbursed by public drug plans for the adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection, only if certain conditions are met.

### Which Patients Are Eligible for Coverage?

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

### What Are the Conditions for Reimbursement?

Opdivo should only be reimbursed if prescribed in an outpatient oncology clinic and supervised and/or delivered in institutions with expertise in delivery of immunotherapy and if the cost of Opdivo is not more than the least costly adjuvant therapy currently funded for this population.

### Why Did We Make This Recommendation?

- Evidence from a clinical trial demonstrated that adjuvant therapy with Opdivo resulted in added clinical benefit in adult patients with stage IIB or IIC melanoma. More patients treated with Opdivo did not have their melanoma return 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, Opdivo may address these needs.
- Based on our assessment of the health economic evidence, Opdivo may represent good value to the health care system at public list prices. The committee determined that there is not enough evidence to justify a greater cost for Opdivo compared with Keytruda, and so the cost of Opdivo should not be greater than the cost of Keytruda.
- Based on public list prices, Opdivo is estimated to lead to cost savings for public drug plans of approximately \$2,284,851 million over the next 3 years. However, the actual budget impact is uncertain.

## Additional Information

### What Is Stage IIB or Stage IIC Melanoma?

Stage IIB or IIC melanoma is a kind of skin cancer in skin cells that produce melanin. The Canadian Cancer Society has estimated that in 2024, 11,300 Canadians will be diagnosed with melanoma skin cancer, and 1,300 people will die from it.



# Summary

## **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 Opdivo Cost?**

Treatment with Opdivo is expected to cost approximately \$9,387 per patient per 28-day cycle.

## Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nivolumab be reimbursed as monotherapy for the adjuvant treatment of adult 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, multicentre, placebo-controlled study (CheckMate-76K; N = 790) demonstrated that adjuvant treatment with nivolumab may result in added clinical benefit for patients with resected stage IIB or IIC cutaneous melanoma. The CheckMate-76K trial showed that administering nivolumab 480 mg every 4 weeks for up to 12 months was associated with statistically significant improvement in recurrence-free survival (RFS) compared to placebo. After a median follow-up of 23.5 months in the nivolumab group and 23.0 months in the placebo group, the median RFS had not been reached in the nivolumab group and was 36.14 months (95% CI, 24.77, not estimable) in the placebo group, corresponding for a hazard ratio (HR) of 0.53 (95% confidence interval [CI], 0.40 to 0.71). The distant metastases-free survival (DMFS) rate at 12 months was 92.0% (95% CI, 89.3 to 94.1) with nivolumab and 88.5% (95% CI, 83.9 to 91.9) with placebo and at 24 months, was 84.0% (95% CI, ■ to ■) with nivolumab and 76.5% (95% CI, ■ to ■) with placebo.

The sponsor-submitted indirect treatment comparisons (ITC) suggested no statistically significant differences in efficacy or harm outcomes between nivolumab and pembrolizumab (currently reimbursed adjuvant systemic therapy for patients with stage IIB and IIC melanoma in Canada) when administered as monotherapy in patients with resected stage IIB or IIC cutaneous melanoma.

Patients identified a need for more effective treatment options without significant long-term side effects. They desired therapies that allow patients to function as best as possible and prevent unnecessary surgical and radiation-impacting quality of life. pERC concluded that nivolumab met some patient needs by providing an additional treatment option with manageable side effects and improved RFS and DMFS after 2 years of follow-up. Conclusions regarding health-related quality of life (HRQoL) outcomes could not be drawn from the CheckMate-76K trial due to the lack of statistical testing and higher dropout rates for patients in the nivolumab group at later time points.

At the sponsor-submitted price for nivolumab and publicly listed price for pembrolizumab, nivolumab was less costly than pembrolizumab. As nivolumab is considered similarly effective as pembrolizumab, the total drug cost of nivolumab should not exceed the total drug cost of pembrolizumab.

**Table 1: Reimbursement Conditions and Reasons**

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
1. Treatment with nivolumab should be reimbursed in adult patients with	In the CheckMate-76K trial, adjuvant therapy with nivolumab demonstrated added clinical	–

Reimbursement condition	Reason	Implementation guidance
completely resected stage IIB or IIC cutaneous melanoma (as defined by the AJCC classification, eighth edition)	benefit for adult patients with resected stage IIB or IIC cutaneous melanoma.	
2. Treatment with nivolumab should be initiated within 12 weeks of surgery	In the CheckMate-76K trial, the benefit of adjuvant therapy with nivolumab was demonstrated in patients treated within 12 weeks after surgery. CADTH reviewed no evidence to support the potential benefits and safety of nivolumab in patients who initiated nivolumab beyond 12 weeks postsurgery.	—
3. Patient must not have received prior treatment beyond complete resection.	Patients enrolled in the CheckMate-76K trial had not been previously treated for melanoma beyond surgical resection for melanoma lesions. As such, the potential benefit of nivolumab in patients who have received prior treatment has not been demonstrated.	—
<b>Discontinuation</b>		
4. Reimbursement of nivolumab should be discontinued in patients who exhibit any of the following: 4.1. clinical or radiological disease recurrence 4.2. evidence of significant toxicity or adverse events potentially related to nivolumab	Treatment with nivolumab in the CheckMate-76K trial was given until disease progression or unacceptable toxicity, whichever occurred first.	—
5. Patients should discontinue treatment following a maximum of 12 months of adjuvant nivolumab	Patients in the CheckMate-76K trial were treated for a maximum of 12 months from first dose of study treatment.	—
<b>Prescribing</b>		
6. Nivolumab should be prescribed in an outpatient oncology clinic and should be supervised and/or delivered in institutions with expertise in the delivery of immunotherapy	To ensure that nivolumab is prescribed only for appropriate patients and that adverse effects are managed optimally and timely.	—
7. Nivolumab should not be combined with other anticancer drugs for melanoma.	Nivolumab was administered as monotherapy in the CheckMate-76K trial. CADTH reviewed no evidence supporting the efficacy and safety of nivolumab in combination with other anticancer drugs for this indication.	—
<b>Pricing</b>		
8. The price of nivolumab should be negotiated so that the total cost of treatment does not exceed the drug program cost of treatment, with the least costly adjuvant therapy	The sponsor-submitted indirect treatment comparison did not provide evidence to support a difference in efficacy or safety between nivolumab and pembrolizumab. As such, there is insufficient evidence to	—

Reimbursement condition	Reason	Implementation guidance
reimbursed for the treatment of adult patients with stage IIB or IIC melanoma following complete resection	justify a cost premium for nivolumab over pembrolizumab. Pembrolizumab is currently the only adjuvant therapy reimbursed for the treatment of adult patients with stage IIB or IIC melanoma following complete resection.	

AJCC = American Joint Committee on Cancer.

## Discussion Points

- pERC agreed with the clinical experts that stage IIB and IIC melanoma following complete resection is associated with a high risk of recurrence and a significant impact on patients' quality of life. Acknowledging that pembrolizumab is the only active adjuvant therapy available in Canada for these patients, pERC agreed with both patients and clinicians that it is important to have an additional drug as an alternative option for this patient population.
- pERC deliberated on the results of the CheckMate-76K trial and noted that 1 year of adjuvant treatment with nivolumab in patients with resected stage IIB or IIC melanoma resulted in a statistically significant improvement in RFS over placebo. The clinical experts consulted by CADTH on this review believed that RFS to be a key outcome in this population. They noted that a between-group difference in RFS of 10% at 1 year would be considered clinically meaningful. They would expect a clinically important effect to increase with time to 15% at 2 years. pERC discussed that the proportion of patients who had not had an RFS event at 12 months was 88.8% (95% CI, 85.6 to 91.2) in the nivolumab group and 81.1% (95% CI, 75.7 to 86.4) in the placebo group, suggesting that the between-group difference at this time point may not be clinically meaningful. At 2 years, this proportion was 76.5% (95% CI, ■ to ■) in the nivolumab group and 60.6% (95% CI, ■ to ■) in the placebo group. pERC agreed with the clinical experts that the RFS results after 2 years of follow-up appeared more clinically relevant.
- pERC discussed that the primary goal of adjuvant therapy in melanoma is to reduce the risk of recurrence and improve overall survival (OS) in patients who have undergone complete surgical resection. pERC noted that, at the most recent data cut-off (February 2023), there were not enough events to analyze OS data, therefore the impact of nivolumab on mortality could not be ascertained. The clinical experts consulted by CADTH noted that mortality would not be expected to be high in this population and that the optimal time point to assess OS would be much longer than the length of follow-up available from the pivotal trial.
- pERC deliberated on the validity of RFS as an acceptable surrogate for OS and agreed with the clinical experts that an improvement in RFS has not been shown to predict improvement in OS in this patient population reliably. However, pERC agreed that RFS may be a meaningful clinical outcome for patients in the adjuvant setting. The clinical experts suggested that it might be reasonable to assume that a reduction in recurrence due to adjuvant treatment with nivolumab will ultimately lead

to improved OS in the long-term; however, it may be challenging to confirm this in a randomized controlled trial.

- pERC discussed the sponsor-submitted ITC and noted that neither of the ITC analyses provided by the sponsor (including a Bayesian network meta-analysis for the primary efficacy analysis and a frequentist analysis using Bucher method to estimate relative harms) provided evidence to support significant differences in efficacy (i.e., RFS) or harms outcomes for nivolumab compared to pembrolizumab for the indication under review. pERC agreed with the CADTH review team that, despite the limitations of the ITC, the claim of no difference between nivolumab compared to pembrolizumab was justified.
- pERC discussed the toxicity profile observed in the CheckMate-76K trial and agreed that the reported adverse events (AEs) appeared to be consistent with the known safety profile of nivolumab. Differences in notable harms between nivolumab and placebo groups were noted, including diarrhea and/or colitis (5.0% versus 1%), hepatitis (4% versus < 1%), rash (9% versus 2%), hypothyroidism/thyroiditis (13% versus < 1%), and hyperthyroidism (8% versus 1%). pERC discussed that, given that diarrhea is a known side effect of nivolumab, there is a risk that this may have resulted in unblinding for those patients experiencing those events. pERC agreed with the CADTH review team that while potential unblinding was likely to impact patient-reported outcomes such as HRQoL, it was less likely to bias results for key outcomes such as RFS and DMFS. A relatively large number of patients also discontinued study treatment in the trial. pERC noted that the difference in treatment discontinuations between the nivolumab (40%) and placebo (27%) groups mainly was accounted for by a difference in withdrawals due to AEs.
- pERC noted that, although patients aged  $\geq 12$  years were eligible for inclusion in the CheckMate-76K trial, the trial included no adolescent patients. The study participants' ages ranged from 19 to 92 years, with a median of 62 years. Acknowledging that the disease characteristics and treatment effects may be similar in adolescent patients with those in adult patients, pERC discussed the appropriateness of generalizing the CheckMate-076 K results to pediatric patients 12 years and older. It acknowledged that the disease characteristics and treatment effects may be similar between adolescent and adult patients. However, both the Health Canada indication and the sponsor's reimbursement request was for adult patients only.

## Background

Melanoma originates from melanocytes, the pigment-producing cells of the skin. It is commonly present in cutaneous primary locations (cutaneous melanoma) but can also arise from melanocytes within the mucosal surfaces of the body (mucosal melanoma) and the uvea of the eye (uveal melanoma) or cutaneous locations in nonhair-bearing surfaces (acral melanoma).

In Canada, melanoma is the fourth most common cancer in those aged 30 to 49 years (7% of all cancer cases). The estimated 25-year person-based prevalence of melanoma in Canada is estimated to be 1

in 399 persons (0.3% of the population in Canada). In 2018, 5.5% (93,890 cases) of all 25-year prevalent cancer cases diagnosed between 1993 and 2017 were melanoma. Based on the 25-year prevalence period, melanoma was the fourth and fifth most prevalent cancer among males and females in Canada, respectively. The estimated incidence of melanoma in Canada for 2022 is 23.5 per 100,000 persons.

Surgical excision is the primary curative treatment for most cases of melanoma, which are identified. According to the Canadian Cancer Society, 10.4% of all new melanomas are stage III at diagnosis, and 3.9% are stage IV (metastatic disease). Although there are no stage-specific survival statistics available in Canada for melanoma, the estimated US-based 5-year survival rate for stage IIB melanoma is 87% and decreases to 82% with stage IIC. Stage IIB/C melanoma patients account for approximately half of patients with stage II melanoma and are at high risk of disease recurrence, with approximately one-third of stage IIB and half of stage IIC patients experiencing recurrence within 5 years after surgery. In addition, some patients with stage IIB/C melanoma have worse survival outcomes than those with stage III, where adjuvant therapy is the standard of care. The decision to pursue adjuvant therapy requires assessment of an individual patient's risk for recurrence. In stage II melanoma specifically, multivariate analysis found that the most relevant prognostic indicators were tumour thickness, presence of ulceration, and anatomic site of the tumour. The primary goal of adjuvant therapy in melanoma is to reduce the risk of recurrence and improve OS in patients who have undergone complete surgical resection but who are considered at high risk for disease recurrence. Currently, pembrolizumab is the only active adjuvant therapy in Canada indicated for patients with stage IIB and IIC melanoma following complete resection, and it is available through restricted benefits with specified criteria in most provinces or territories.

Nivolumab is a humanized IgG4 monoclonal antibody immune checkpoint inhibitor that targets the programmed cell death (PD)-1 receptor, preventing PD-1 from inhibiting the immune response to tumours. Health Canada has approved it for the adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection. The Notice of Compliance was received on December 29, 2023. Nivolumab is also indicated for melanoma with regional lymph node involvement or metastatic melanoma, as well as classical Hodgkin Lymphoma and various colorectal, renal, lung, head and neck, esophageal, gastric and urothelial carcinomas. Nivolumab is administered as an IV infusion over 30 minutes. The recommended dosage for adjuvant treatment of adult patients with stage IIB or IIC is 240 mg every 2 weeks or 480 mg every 4 weeks, until disease recurrence or unacceptable toxicity, up to 1 year.

## Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized controlled trial in patients with completely resected stage IIB and IIC melanoma; and ITC conducted for the comparisons of efficacy and safety of nivolumab versus pembrolizumab
- patients' perspectives gathered by 2 patient group(s), Melanoma Canada and Save Your Skin Foundation



- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise in diagnosing and treating patients with stage IIB/IIC melanoma
- input from 1 clinician group, Ontario Health - Cancer Care Ontario (OH-CCO) Skin Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

## Stakeholder Perspectives

### Patient Input

Input was received from 2 patient groups, Melanoma Canada and Save Your Skin Foundation (SYSF). Both groups gathered data through online surveys, with a sample of 172 patients and 15 caregivers.

Patients described a variety of impacts from their condition, including fear, anxiety, confusion, scarring and disfigurement of skin, disrupted sleep, as well as pain, fatigue and depression.

Patients identified a need for more treatment options, given that there is only 1 drug approved for this indication, pembrolizumab, and noted that the risk of recurrence with stage IIB/IIC was higher than with stage IIIA. A total of 22 patients, including 20 participants from the Melanoma Canada survey and 2 participants from the SYSF survey, indicated they had been treated with adjuvant therapy for stage IIB or IIC melanoma. A common issue reported by the Melanoma Canada survey participants was the length of time and cost of travel to get to a clinical trial site for treatment with nivolumab. Of those treated, 73% of 15 respondents indicated the side effects were worth the treatment, and 27% stated the side effects were not worth the treatment. One of the 2 patients from the SYSF survey who reported having experience with nivolumab indicated that they believed the benefit from nivolumab was worth the side effects, but the other patient-reported challenges with missing work due to travel requirements for accessing nivolumab.

### Clinician Input

#### Input From Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH on this review noted the need for other immunotherapies with better efficacy. The clinical experts differed on their opinions of nivolumab, with 1 seeing it as a clear improvement over pembrolizumab, while the other saw it as similar in efficacy and harms to pembrolizumab.

The clinical experts noted that the patients best suited for nivolumab would be those with low Eastern Cooperative Oncology Group (ECOG) status, no comorbidities or active autoimmune conditions, and those who are at significant risk of relapse.

The response would be assessed through a physical exam and periodic imaging (PET-CT or whole-body CT with MRI of the head). The decision to discontinue therapy would be prompted by evidence of recurrence, regional or distant metastases, or drug intolerance.

## Clinician Group Input

CADTH received 1 clinician group submission from the Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee (OH-CCO's DAC).

There were no significant areas of disagreement between the clinician group and the clinical experts consulted by CADTH on this review.

The clinician group and the clinical experts agreed that RFS and DMFS are key outcomes for these patients, and it is important to have an additional drug for this population of patients, as pembrolizumab is the only current option. The clinician group noted the difference in dosing between nivolumab (every 2 or 4 weeks) and pembrolizumab (every 3 or 6 weeks). The clinician groups agreed with the clinical experts that the most appropriate patients to receive the drug would reflect those enrolled in CheckMate-76K.

## Drug Program Input

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
<b>Relevant comparators</b>	
Phase III, global, double-blind, randomized, CheckMate-76K Trial compared nivolumab to placebo, appropriate at the time. Pembrolizumab is now indicated for this population. Nivolumab will be positioned as an additional adjuvant therapy option in this space; there will be no shift in the current treatment paradigm.	Comment from the drug programs to inform pERC deliberations.
<b>Considerations for initiation of therapy</b>	
PAG notes CheckMate-76K references the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition, for disease staging. <b>Would other classification systems be applicable?</b> In CheckMate-76K, patients were randomized to receive either nivolumab or placebo within 12 weeks after surgery. <b>What is considered the maximum time frame for postsurgical resection to initiate nivolumab?</b>	The clinical expert did not believe other classification systems would apply and noted that the 8th Edition of the AJCC Cancer Staging Manual is the current standard. According to the clinical experts, the maximum time frame after surgery in clinical practice is 12 weeks. One clinical expert noted that occasionally, extenuating circumstances may prompt a physician to still offer treatment beyond this time frame, with the understanding that the evidence is based on treatment being initiated within 12 weeks postsurgery. pERC agreed that nivolumab should be initiated within 12 weeks of surgery. This is aligned with the pivotal trial criteria and clinical practice.
In CheckMate-76K, placebo-treated patients who experienced disease recurrence within 3 years after the last dose of placebo and nivolumab-treated patients who experienced recurrence greater than 6 months and within 3 years after completing treatment were eligible to cross over	pERC agreed with the clinical experts that the same principle used for other solid tumours could be applied in this case, according to the common standard clinical practice.

Implementation issues	Response
<p>or rechallenge with nivolumab. Patients with recurrent, resectable disease were offered nivolumab for a maximum of 12 months.</p> <p>Patients in other solid tumours (e.g., lung, melanoma) are eligible for downstream PD-1/PD-L1 inhibitor provided that disease recurrence (whether locoregional or distant) occurs more than 6 months from the last dose of adjuvant PD-1/PD-L1 inhibitor. <b>Can the same principle be applied in this setting?</b></p>	
<b>Considerations for discontinuation of therapy</b>	
<p><b>If treatment interruptions occur, should the remainder of the doses be given even if it will take more than a calendar year to deliver the treatments, provided there has been no disease progression in between?</b></p> <p>For example:</p> <p>a) The patient received 2 months' of doses but had to take 5 months off. <b>Should the remaining 10 months' worth of doses be given when the patient resumes treatment?</b></p> <p>b) The patient received 10 months' of doses but had to take 5 months off. <b>Should the remaining 2 months' doses be given when the patient resumes treatment?</b></p>	<p>The clinical experts noted that the principle of adjuvant therapy is to start and complete the treatment promptly and uninterruptedly. pERC agreed with the clinical experts that decisions regarding treatment interruptions would depend on the clinical circumstances and that decisions for discontinuing adjuvant therapy should be made on a case-by-case basis by the treating physician after a discussion of the pros and cons with the patient. pERC agreed that the course of treatment could go beyond 12 months, depending on the clinical situation.</p>
<b>Considerations for prescribing therapy</b>	
<p>PAG would like to inform pERC that jurisdictions will implement weight-based dosing up to a cap, similar to other immunotherapy policies (i.e., nivolumab 3 mg/kg up to 240 mg every 2 weeks or nivolumab 6 mg/kg up to 480 mg every 4 weeks).</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>
<b>Generalizability</b>	
<p><b>Should patients with noncutaneous melanoma be considered for treatment with nivolumab for this indication?</b> (current Pembrolizumab indication for this population allows stage IIB and IIC cutaneous or mucosal melanoma and excludes ocular or uveal melanoma)</p> <p><b>Should patients with ECOG performance status of 2 or greater be eligible for nivolumab for this indication?</b></p>	<p>The clinical experts believed that patients with uveal and ocular melanoma should be excluded. pERC agreed with the clinical experts.</p> <p>The clinical experts consulted for this review believed that patients with an ECOG performance status of 2 or greater should be eligible to receive nivolumab if the diminished performance status is due to comorbidities unlikely to be life-threatening in the foreseeable future. One clinical expert noted that no active disease is being treated in adjuvant therapy; therefore, treating patients with ECOG performance status of 2 or more with nivolumab would be unlikely.</p> <p>pERC acknowledged that clinicians may consider using nivolumab at their discretion for patients with an ECOG performance status of 2 or greater.</p>
<p>PAG notes that pembrolizumab is currently available for this population.</p>	<p>Comment from the drug programs to inform pERC deliberations.</p>

Implementation issues	Response
<b>Care provision issues</b>	
Nivolumab is already prepared and administered at facilities throughout Canada. Health care professionals have extensive experience with it. Preparation and administration time for nivolumab are relatively reasonable and would not be expected to significantly increase health system resources.	Comment from the drug programs to inform pERC deliberations.
<b>System and economic issues</b>	
PAG notes that pembrolizumab has confidential pricing.	Comment from the drug programs to inform pERC deliberations.

ECOG = Eastern Cooperative Oncology Group; PAG = Provincial Advisory Group; PD-1 = Programmed death-1 receptor; PD-L1 = Programmed death ligand-1.

## Clinical Evidence

### Systematic Review

#### Description of Studies

CheckMate-76K is a phase III, randomized, double-blind, multicentre clinical trial designed to evaluate the efficacy and safety of nivolumab in wholly resected stage IIB and IIC melanoma across 20 countries and 132 locations, including Canada.<sup>13</sup> Adults and children  $\geq 12$  years of age were eligible for enrolment. A total of 790 patients were randomly assigned in a 2:1 ratio to receive 480 mg of nivolumab ( $n = 526$ ) or placebo ( $n = 264$ ). Patients in the treatment groups were treated with nivolumab 480 mg every 4 weeks via 30-minute IV infusions or a matched-administration placebo. Placebo-treated patients who experienced disease recurrence within 3 years after the last dose of placebo and nivolumab-treated patients who experienced recurrence greater than 6 months and within 3 years after completing treatment were eligible to receive on-study open-label nivolumab treatment. The primary objective of CheckMate-76K was to compare the efficacy, as measured by investigator-assessed RFS, provided by nivolumab monotherapy versus placebo in patients with completely resected stage IIB and IIC melanoma with no evidence of disease who are at high risk for recurrence.<sup>14</sup> The secondary objectives were to compare OS and DMFS between the 2 treatment groups, assess nivolumab's safety and toxicity, and evaluate investigator-assessed outcomes on next-line therapies.

Overall, the enrolled patient population generally represented a stage II melanoma population, with a median age of 62 years and more males (61.2%) than females (38.8%). The majority of patients had stage IIB melanoma (60.1%) (American Joint Committee on Cancer [AJCC], 8th edition). The mean time from local-wide excision surgery to randomization was [REDACTED]. Although patients aged  $\geq 12$  years were eligible for enrolment, no adolescents were randomized. Generally, baseline demographic and disease characteristics were well balanced between the nivolumab and placebo groups.

#### Efficacy Results

##### *Recurrence-Free Survival*

At the data cut-off date of 28 June 2022, the median follow-up for all randomized patients was 15.84 months for the nivolumab arm and 15.93 months for the placebo group. At the data cut-off date of 21 February 2023,

the median follow-up for all randomized patients was 23.5 months for the nivolumab group and 23.0 months for the placebo group.

At the first interim analysis 1 (IA1, data cut-off of June 28, 2022), a median RFS had not been reached in either group for an HR of 0.42 (95% CI, 0.30 to 0.59),  $P < 0.0001$ . At the most recent data cut-off date of February 21, 2023, 186 RFS events had occurred (complete information fraction). The median RFS had not been reached in the nivolumab group and was 36.14 months (95% CI, 24.77, not estimable) in the placebo group, for an HR of 0.53 (95% CI, 0.40 to 0.71).

At a data cut-off date of June 28, 2022, the RFS rate was 89.0% (95% CI, 85.6 to 91.6) and 79.4% (95% CI, 73.5 to 84.1) in nivolumab and placebo, respectively. At the February 21, 2023, data cut-off, the RFS rate was largely unchanged from IA1, 88.8% (95% CI, 85.6 to 91.2) and 81.1% (95% CI, 75.7 to 86.4) at 12 months, for nivolumab and placebo. At 24 months, which was only reported at IA2, the RFS rates were 76.5% (95% CI, ■■■■■) and 60.6% (95% CI, ■■■■■) in the nivolumab and placebo groups, respectively.

### ***Overall Survival***

At the time of the most recent February 21, 2023, data cut-off, the prespecified number of events for the OS interim analysis had not been reached, so no data were reported.

### ***Distant Metastases-Free Survival***

At IA1, with a data cut-off of June 28, 2022, a median DMFS had not been reached in either group, with 8.0% of patients in the nivolumab group having experienced an event and 15.5% of patients experiencing an event in the placebo group, for an HR of 0.47 (95% CI, 0.30 to 0.72). The DMFS rate at 12 months was ■■■ (95% CI, 89.3 to ■■■) in the nivolumab group and ■■■ (95% CI, ■■■ to ■■■) in the placebo group. At the most recent data cut-off, February 21, 2023, a median DMFS was still not reached in the nivolumab group and was 36.14 months (95% CI, 32.85, N/A) in the placebo group, with 13.1% of patients in the nivolumab group and 19.3% of patients in the placebo group experiencing an event, for an HR of 0.62 (95% CI, 0.43 to 0.89). The DMFS rate at 12 months was 92.0% (95% CI, 89.3 to 94.1) with nivolumab and 88.5% (95% CI, 83.9 to 91.9) with placebo and at 24 months, was 84% (95% CI, ■■■ to ■■■) with nivolumab and was 76% (95% CI, ■■■ to ■■■) with placebo.

### ***Progression-Free Survival 2***

A median progression-free survival (PFS) was not reached as of the most recent data, February 21, 2023. In all randomized patients, 40 (7.6%) PFS2 events had occurred in the nivolumab group, and 31 (11.7%) PFS2 events had happened in the placebo group, for an HR of 0.63 (95% CI, 0.40 to 1.01).

### ***Health-Related Quality of Life***

HRQoL was an exploratory outcome in CheckMate-76 76K and was assessed using the EORTC QLQ-C30 and EQ-5D-5L instruments. None of the within-group changes from baseline over time in the study exceeded the MID for the instrument.

## Harms Results

There were 96% of patients in the nivolumab group and 88% of patients in the placebo group who reported an AE (all-cause), with 23% and 12% of patients, respectively, reporting a grade 3 or 4 AE. The most common AE, nivolumab versus placebo, were fatigue (■ versus ■), diarrhea (■ versus ■) and pruritus (■ versus ■). Hypothyroidism was reported in 12% of patients in the nivolumab group and no patients in the placebo group.

15% of patients in the nivolumab group and 11% of patients in the placebo group reported a serious adverse event (SAE), but no specific SAEs occurred in 1% or more of patients.

There were 18% of patients in the nivolumab group and 4% of patients in the placebo group who discontinued due to an AE, and 7% versus 1% who withdrew due to a grade 3 or 4 AE, respectively. The most common reason for discontinuation was [REDACTED]

Notable harms identified by the clinical experts consulted by CADTH on this review included diarrhea (particularly grade 3 or 4), diabetes mellitus, and arthritis. Grade 3 or 4 diarrhea/colitis events occurred in 2% of nivolumab patients and less than 1% of placebo patients, while diabetes occurred in less than 1% of nivolumab patients and no placebo patients, and arthritis in |||| of nivolumab and |||| placebo patients.

## Critical Appraisal

Concerning internal validity, CHECKMATE-76K appears to have been a reasonably well-conducted trial, with adequate procedures for randomization and blinding. A relatively large number of patients discontinued study treatment, and there was a difference in treatment discontinuations between the nivolumab (40%) and placebo (27%) groups. This difference was mostly accounted for by a difference in withdrawals due to AE, and this may have biased the analysis of efficacy and harms.

Concerning external validity, CheckMate-76K was not of sufficient duration to assess OS, as the clinical experts believed that a follow-up of at least 5 years would be needed for such an analysis to occur. The clinical experts also believed that RFS, the primary outcome, is better assessed at a later time than was reported in the trial. There was also no active comparator in CheckMate-76K, the most appropriate choice being pembrolizumab.

## GRADE Summary of Findings and Certainty of the Evidence






The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

RFS (1, 2, and 3 years follow-up), OS (5 years follow-up), DMFS (1, 2, and 3 years follow-up)

notable harms: diarrhea (grade 3 or 4), diabetes mellitus, arthritis (all reported within 100 days of last study dose).

**Table 3: Summary of Findings for Adjuvant Nivolumab Versus Placebo for Patients With Stage IIB/IIC Resected Melanoma**

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Nivolumab	Placebo			
<b>OS</b>							
OS (secondary outcome) Follow-up: 5 years	790 (1 RCT)	NR	NR	NR	NR	n/a <sup>a</sup>	Cannot be assessed
<b>RFS</b>							
RFS (primary outcome) Follow-up: 1 year Data cut-off: June 2022	790 (1 RCT)	0.42 (0.30 to 0.59)	89.0 (85.6 to 91.6)	79.4 (73.5 to 84.1)	NR	Low <sup>b</sup>	Nivolumab may result in an improvement in RFS when compared to placebo after 1 year follow-up
Follow-up: 2 years Data cut-off: February 2023	790 (1 RCT)	0.53 (0.40 to 0.71)	76.5 (████████)	60.6 (████████)	NR	Low <sup>b</sup>	Nivolumab may result in an improvement in RFS when compared to placebo after 2 years follow-up
Follow-up: 3 years Data cut-off: February 2023	790 (1 RCT)	████████	████████	████████	NR	Very low <sup>c</sup>	The evidence is very uncertain about the effects of nivolumab on RFS when compared to placebo after 3 years follow-up
<b>DMFS</b>							
DMFS (secondary outcome) Follow-up: 1 year Data cut-off: June 2022	790 (1 RCT)	0.47 (0.30 to 0.72)	████████	██ (████████)	NR	Low <sup>b</sup>	Nivolumab may result in an improvement in DMFS when compared to placebo after 1 year follow-up

Outcome measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Nivolumab	Placebo			
Follow-up: 2 years Data cut-off: February 2023	790 (1 RCT)	0.62 (0.43 to 0.89)			NR	Low <sup>b</sup>	Nivolumab may result in an improvement in DMFS when compared to placebo after 2 years follow-up
Follow-up: 3 years Data cut-off: February 2023	790 (1 RCT)				NR	Very low <sup>c</sup>	The evidence is very uncertain about the effects of nivolumab on DMFS when compared to placebo after 3 years follow-up
<b>HARMS</b>							
Diarrhea (grade 3 to 4) Follow-up: within 100 days of last dose	790 (1 RCT)	NR	13 per 1,000	None	NR	Very low <sup>d</sup>	The evidence is very uncertain regarding whether nivolumab increases risk of Grade 3 to 4 diarrhea when compared to placebo
Diabetes mellitus Follow-up: within 100 days of last dose	790 (1 RCT)	NR	6 per 1,000	None	NR	Very low <sup>d</sup>	The evidence is very uncertain regarding whether nivolumab increases the risk of diabetes mellitus when compared to a placebo
Arthritis Follow-up: within 100 days of last dose	790 (1 RCT)	NR	25 per 1,000	4 per 1,000	NR	Very low <sup>d</sup>	The evidence is very uncertain regarding whether nivolumab increases the risk of arthritis when compared to a placebo

CI = confidence interval; DMFS = distant metastasis-free survival; N/A = not available; NR = not reported; OS = overall survival; RCT = randomized controlled trial; RFS = recurrence-free survival.



<sup>a</sup>Could not be rated because no effect estimates were available for this time point.

<sup>b</sup>Rated down 2 levels; once for serious concerns over imprecision as unable to conclusively determine whether between-group difference met the MID and once for serious concerns over the risk of bias due to large differences in treatment discontinuations between groups.

<sup>c</sup>Rated down 3 levels: twice for very serious concerns over imprecision, including low sample size and failure to meet MID and once for serious concerns over the risk of bias due to large differences in treatment discontinuations between groups.

<sup>d</sup>Rated down 3 levels: twice for very serious concerns over imprecision for not meeting the MID and unknown whether it reached null and once for serious concerns over the risk of bias due to large differences in treatment discontinuations between groups.

Note in CheckMate-76K, only OS and RFS were part of the multiple testing procedure (MTP), and none of the data points reported in the above table were part of the MTP as they were specifically reported for the GRADE analysis.

## Indirect Comparisons

### Description of Studies

The sponsor conducted a systematic literature review in November 2022 to identify evidence for inclusion in a network meta-analysis (NMA) and a Bucher method ITC in patients with nonmetastatic resected stage IIB/C cutaneous melanoma.

CheckMate-76K included 790 randomized patients, and KEYNOTE-716 included 976 randomized patients. Both trials were double-blind, placebo-controlled, and included an international, multicentre population.

### Efficacy Results

For CheckMate-76K, data-informed analyses were based on an updated analysis from April 2023 with a minimum follow-up of 15.6 months and a median follow-up of 23.0 months in both treatment arms (23.5 for nivolumab and 23.1 for placebo). One efficacy outcome, RFS, was included in these analyses. The assessment of proportional hazards demonstrated evidence of a violation of the proportional hazards assumption, and therefore, the time-varying models are reported as the base case. There was no evidence for a difference in RFS between nivolumab and pembrolizumab at all time points.

### Harms Results

In the results of the Bucher ITC for treatment-related AEs, there were no significant differences in the odds of treatment-related grade of at least 3 AE incidence (OR [95% CI], 1.09 [0.41 to 2.94]) or treatment-related any-grade AE incidence (1.55 [0.99 to 2.43]) between nivolumab and pembrolizumab.

### Critical Appraisal

The sponsor conducted an NMA using a Bayesian approach with fixed effects models for the primary efficacy analysis, and a frequentist approach was applied using the Bucher method to estimate relative harms. Both these methods were appropriate given the limited availability of data.

The main limitation of the NMA is that it contained a very small amount of data from only 2 studies. Efficacy assessment was limited to a single outcome (RFS), and it would have been informative to include other efficacy outcomes. Follow-up time was also limited to 23 months and 39 months in the CheckMate-76K and Keynote-716 studies, respectively. Therefore, results beyond 23 months would be less reliable and subject to increasingly greater extrapolation as time points become longer. In addition, the differential follow-up times for the studies exacerbate the uncertainty in the comparisons for later time points in the analyses. Efficacy assessment was limited to a single outcome (RFS), and it would have been informative to include other efficacy outcomes. A strength of the comparisons made within the NMA and the Bucher analyses was that the studies were similar in design and population characteristics.

Despite some differences in population characteristics between the 2 trials, the sponsor assumed that AJCC stage, administration frequency, and treatment history were not effect modifiers. The clinical experts consulted by CADTH for this review believed this was a reasonable assumption.

To align definitions of recurrence between these 2 trials, an alternative definition of RFS was explored for CheckMate-76K, omitting malignant melanoma in situ and new primary invasive melanoma. The results of this sensitivity analysis were consistent with the base-case analysis.

No significant differences were observed between nivolumab and pembrolizumab for RFS.

No significant differences were observed between nivolumab and pembrolizumab for treatment-related AEs (any grade, grade  $\geq 3$ ). The sponsor stated that all-cause AEs were an outcome of interest, but no analyses of this outcome were provided, and the sponsor did not provide an explanation for this omission. This would have been informative, given the trends observed in the treatment-related AE analyses (Table 28).

Neither the NMA nor the Bucher analysis provided evidence of a difference in efficacy or harm outcomes for nivolumab compared to pembrolizumab in patients with nonmetastatic resected stage IIB/C cutaneous melanoma.

## Economic Evidence

### Cost and Cost-Effectiveness

**Table 4: Summary of Economic Information**

Component	Description
Type of economic evaluation	Cost minimization analysis
Target population	As adjuvant treatment in patients with stage IIB/IIC resected melanoma.
Treatment	Nivolumab as adjuvant treatment to resection.
Dose regimen	3 mg/kg (max 240 mg) every 14 days or 6 mg/kg (max 480 mg) every 28 days. <sup>a</sup>
Submitted price	Nivolumab, 40 mg/4 mL vial: \$782.22 Nivolumab, 100 mg/10 mL vial: \$1,955.56
Submitted treatment cost	\$9,387 per patient per 28-days
Comparator	Pembrolizumab as adjuvant treatment to resection.
Perspective	Canadian publicly funded health care payer
Time horizon	1 year
Key data source	CheckMate 76K double-blind, randomized controlled trial comparing nivolumab to placebo. One sponsor-conducted network meta-analysis comparing nivolumab to pembrolizumab.
Costs considered	Drug acquisition costs, administration costs, subsequent treatment costs, subsequent treatment administration costs. Monitoring costs and adverse event costs were considered in a scenario analysis.

Component	Description
<b>Key limitations</b>	<ul style="list-style-type: none"> <li>The sponsor's indirect comparison was associated with some uncertainty due to limitations within the submitted NMA and its associated imprecision, as well as the likelihood that different dosing for both comparators will be used in clinical practice than in the clinical trials and thus the NMA. However, the limitations were not expected to impact the claim of clinical similarity.</li> <li>Confidential pricing agreements exist for pembrolizumab for this indication and nivolumab for another melanoma indication.</li> </ul>
<b>CADTH reanalysis results</b>	<p>CADTH did not undertake a base case reanalysis. Based on the public list prices, nivolumab remains cost-saving compared with pembrolizumab.</p> <p>CADTH could not address the existence of confidential pricing for both products.</p> <p>If nivolumab is considered similar to pembrolizumab in terms of efficacy and safety, the extent to which savings will be realized with the use of nivolumab compared to pembrolizumab is dependent on patient weight.</p>

\*The dosing in the Product Monograph recommends a fixed dose of 240 mg every 14 days or 480 mg every 28 days. As noted by the sponsor and CADTH, which is participating in public drug plans, weight-based dosing is implemented in Canada.

## Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the inclusion of administration costs was inappropriate as submitted budget impact analyses (BIAs) should be from the perspective of the public drug plan payer, the market shares of pembrolizumab and nivolumab may be overestimated as some patients are still likely to undergo active surveillance rather than receive adjuvant therapy, the uptake of nivolumab relative to pembrolizumab is uncertain, and the price of drugs paid by public plans is uncertain as confidential pricing is likely in place.

CADTH reanalyses excluded administration costs. In the CADTH base case, the budget impact of nivolumab as adjuvant treatment of adult patients with stage IIB or IIC melanoma following complete resection is expected to result in cost savings of \$540,130 in year 1, \$867,977 in year 2, and \$876,743 in year 3, for a 3-year total cost savings of \$2,284,851. Uncertainty remains in the extent to which nivolumab will displace pembrolizumab and the price paid by public plans for pembrolizumab.

## pERC Information

### Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung; Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

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**Regrets:** None

**Conflicts of interest:** None



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