Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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

Recommendation: Reimburse with Conditions

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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, multi-centre, 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 administration of 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 [redacted] to [redacted]) with nivolumab and 76.5% (95% CI: [redacted] to [redacted]) with placebo.

The sponsor-submitted indirect treatment comparisons (ITC) suggested no statistically significant differences in efficacy or harms 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 two 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
Initiation		
1. Treatment with nivolumab should be reimbursed in adult patients with completely resected stage IIB or IIC cutaneous melanoma (as defined by the AJCC classification, eighth edition)	In the CheckMate-76K trial, adjuvant therapy with nivolumab demonstrated added clinical 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 post-surgery.	—
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 lesion. As such, the potential benefit of nivolumab in patients who have received prior treatment has not been demonstrated.	—
Discontinuation		
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.	—
Prescribing		
6. Nivolumab 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 nivolumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
7. Nivolumab should not be used in combination 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	—

Reimbursement condition	Reason	Implementation guidance
	combination with other anticancer drugs for this indication.	
Pricing		
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 reimbursed for the treatment of adult patients with Stage IIB or IIC melanoma following complete resection	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 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 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 and 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 timepoint may not be clinically meaningful. At 2 years, this proportion was 76.5% (95% CI: [redacted] to [redacted]) in the nivolumab group and 60.6% (95% CI: [redacted] to [redacted]) in the placebo group. pERC agreed with the clinical experts that the RFS results after 2 years of follow-up appeared to be more clinically relevant.
- pERC discussed that the primary goal of adjuvant therapy in melanoma is to reduce 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 for an analysis of overall survival (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 that is 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 reliably predict improvement in OS in this patient population. 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 an improvement in OS in the long term; however, it may be challenging to confirm this in a randomized controlled trial.
- pERC discussed the sponsor-submitted indirect treatment comparisons (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. There was also a relatively large number of patients who discontinued study treatment in the trial. pERC noted that the difference in treatment discontinuations between the nivolumab (40%) and placebo (27%) groups was mostly accounted for by a difference in withdrawals due to AEs.

- pERC noted that, although patients aged ≥12 years were eligible for inclusion in the CheckMate-76K trial, the trial included no adolescent patients. The study participants' age 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 and 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, which are the pigment-producing cells of the skin, 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 one in 399 persons (0.3% of the Canadian population). 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 five 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 tumor. The primary goal of adjuvant therapy in melanoma is to reduce risk of recurrence and improve overall survival (OS) in patients who have undergone complete surgical resection, but who are considered 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 benefit with specified criteria in most provinces/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. It has been approved by Health Canada for the adjuvant treatment of adult patients with Stage IIB or IIC melanoma following complete resection. The Notice of Compliance (NOC) 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, various colorectal, renal, lung, head and neck, esophageal, gastric and urothelial carcinomas. Nivolumab is administered as an intravenous 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 indirect treatment comparisons 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 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 two patient groups, Melanoma Canada and Save Your Skin Foundation (SYSF), and 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 one drug approved for this indication, pembrolizumab, and noted that the risk of recurrence with stage IIB/IIC was actually 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% indicated the side effects were not worth the treatment. One of the 2 patients from the SYSF survey who reported having experience with nivolumab stated 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 that have better efficacy. The clinical experts differed on their opinions of nivolumab, with one seeing it as a clear improvement over pembrolizumab, while the other saw it as being 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 co-morbidities or active autoimmune conditions, and those who are at significant risk of relapse.

Response would be assessed through physical exam and periodic imaging (positron emission tomography-computerized axial tomography [PET-CT] or whole-body CT with magnetic resonance imaging [MRI] of 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 two or four weeks) and pembrolizumab (every three or six weeks). The clinician groups agreed with the clinical experts that the most appropriate patients to receive the drug would reflect those enrolled into 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
Relevant comparators	
Phase 3, 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.
Considerations for initiation of therapy	
PAG notes Checkmate-76K references the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition for disease staging. **Would other classification systems be applicable?** In CheckMate-76K, patients were randomized to receive either nivolumab or placebo within 12 weeks after surgery. **What is considered the maximum time frame post-surgical resection to initiate nivolumab?**	The clinical expert did not believe that 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, in clinical practice, the maximum time frame after surgery would be 12 weeks. One clinical expert noted that occasionally there may be extenuating circumstances that 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 post-surgery. pERC agreed that nivolumab should be initiated within the 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 or rechallenge with nivolumab. Patients with recurrent, resectable disease were offered nivolumab for a maximum duration of 12 months. In other solid tumours (e.g., lung, melanoma), patients 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. **Can the same principle be applied in this setting?**	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.
Considerations for discontinuation of therapy	
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? For example: a) The patient has received 2 months' worth of doses but had to take 5 months off. **Should the remaining 10**	The clinical experts noted that the principle of adjuvant therapy is to start and complete the treatment in a timely and uninterrupted manner. pERC agreed with the clinical experts that the decisions regarding treatment interruptions would depend on the clinical circumstances, and that decisions for discontinuation of adjuvant therapy should be made on a case-by-case basis by the treating physician, after a discussion of the pros and cons

Implementation issues	Response
months' worth of doses be given when the patient resumes treatment? b) The patient has received 10 months' worth of doses but had to take 5 months off. **Should the remaining 2 months' worth of doses be given when the patient resumes treatment?**	with the patient. pERC agreed the course of treatment could go beyond 12 months depending on the clinical situation.
Considerations for prescribing of therapy	
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 3mg/kg up to 240mg every 2 weeks or nivolumab 6mg/kg up to 480mg every 4 weeks.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Should patients with non-cutaneous melanoma be considered for treatment with nivolumab for this indication? (current Pembrolizumab indication for this population allows Stage IIB and IIC cutaneous or mucosal melanoma, and excludes ocular or uveal melanoma) **Should patients with ECOG performance status of 2 or greater be eligible for nivolumab for this indication?**	The clinical experts believed that patients with uveal and ocular melanoma should be excluded. pERC agreed with the clinical experts. The clinical experts consulted by CADTH believed that patients with an ECOG performance status of 2 or greater should be eligible to receive nivolumab for if the diminished performance status is due to co-morbidities that are unlikely to be life-threatening in the foreseeable future. One clinical expert noted that no active disease is being treated in the adjuvant therapy setting; therefore, treating patients who have ECOG performance status of 2 or more with nivolumab would be unlikely. pERC acknowledged that clinicians may consider using nivolumab for patients with an ECOG performance status of 2 or greater at their discretion.
PAG notes that pembrolizumab is currently available for this population.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
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 create a significant increase to health system resources.	Comment from the drug programs to inform pERC deliberations.
System and economic issues	
PAG notes that there is confidential pricing for pembrolizumab.	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 3, randomized, double-blind, multi-center clinical trial designed to evaluate the efficacy and safety of nivolumab in completely resected stage IIB and IIC melanoma across 20 countries and 132 locations, including Canada.[13] Adults

and children ≥ 12 years of age were eligible for enrollment. 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 recurrence-free survival (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.[14] The secondary objectives were to compare OS and distant metastases-free survival (DMFS) between the two treatment groups, assess the safety and toxicity of nivolumab and evaluate investigator-assessed outcomes on next-line therapies.

Overall, the enrolled patient population was generally representative of 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 ≥12 years were eligible for enrollment, no adolescents were randomized. Generally, baseline demographic and disease characteristics were well balanced between the nivolumab and placebo groups.

Efficacy Results

RFS

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 a HR of 0.42 (95% CI: 0.30 to 0.59), p<0.0001. At the most recent data cut-off date of Feb 21, 2023, 186 RFS events had occurred (complete information fraction), and 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 a HR of 0.53 (95% CI: 0.40 to 0.71).

*A*t 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 Feb 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: [redacted]) and 60.6% (95% CI: [redacted]) in the nivolumab and placebo groups, respectively.

OS

At the time of the most recent Feb 21, 2023, data cut-off, the pre-specified number of events for the OS interim analysis had not been reached, and as a result, there are no data reported.

DMFS

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 a HR of 0.47 (95% CI: 0.30 to 0.72). The DMFS rate at 12 months was [redacted] (95% CI: 89.3 to [redacted]) in the nivolumab group and [redacted] (95% CI: [redacted] to [redacted]) 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 a 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 [redacted] to [redacted]) with nivolumab and was 76% (95% CI: [redacted] to [redacted]) with placebo.

PFS2

A median PFS had not been reached as of the most recent data, Feb 21, 2023. In all randomized patients, 40 (7.6%) PFS2 events had occurred in the nivolumab group and 31 (11.7%) PFS2 events had occurred in the placebo group, for a HR of 0.63 (95% CI 0.40 to 1.01).

HRQOL

HRQOL was an exploratory outcome in CHECKMATE 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 ([redacted] versus [redacted]), diarrhea ([redacted] versus [redacted]) and pruritus ([redacted] versus [redacted]). Hypothyroidism was reported in 12% of patients in the nivolumab group and no patients in the placebo group.

There were 15% of patients in the nivolumab group and 11% of patients in the placebo group who reported a SAE. There were no specific SAEs that 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 events of diarrhea/colitis occurred in 2% of nivolumab patients and <1% of placebo patients, while diabetes occurred in <1% of nivolumab patients and no placebo patients and arthritis in [redacted] of nivolumab and [redacted] placebo.

Critical Appraisal

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

With respect to 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 were of the opinion that RFS, the primary outcome, is better assessed at a later time point 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 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			
OS							
OS (secondary outcome) ***Follow-up: 5 years***	790 (1 RCT)	NR	NR	NR	NR	n/a[a]	Cannot be assessed
RFS							
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[b]	Nivolumab may result in an improvement in RFS when compared to placebo after 1 year follow-up
Follow-up: 2 years ***Data cut-off: Feb 2023***	790 (1 RCT)	0.53 (0.40 to 0.71)	76.5 ([redacted])	60.6 ([redacted])	NR	Low[b]	Nivolumab may result in an improvement in RFS when compared to placebo after 2 years follow-up
Follow-up: 3 years ***Data cut-off: Feb 2023***	790 (1 RCT)	[redacted]	[redacted]	[redacted]	NR	Very low[c]	The evidence is very uncertain about the effects of nivolumab on RFS when compared to placebo after 3 years follow-up
DMFS							
DMFS (secondary outcome) Follow-up: 1 year ***Data cut-off: June 2022***	790 (1 RCT)	0.47 (0.30 to 0.72)	[redacted])	[redacted] ([redacted])	NR	Low[b]	Nivolumab may result in an improvement in DFMS when compared to placebo after 1 year follow-up
Follow-up: 2 years ***Data cut-off: Feb 2023***	790 (1 RCT)	0.62 (0.43 to 0.89)	[redacted] ([redacted])	[redacted] ([redacted])	NR	Low[b]	Nivolumab may result in an improvement in DMFS when compared to placebo after 2 years follow-up
Follow-up: 3 years ***Data cut-off: Feb 2023***	790 (1 RCT)	[redacted]	[redacted]	[redacted]	NR	Very low[c]	The evidence is very uncertain about the effects of nivolumab on DMFS when compared to placebo after 3 years follow-up
HARMS							
Diarrhea (grade 3-4) Follow-up: within 100 days of last dose	790 (1 RCT)	NR	13 per 1000	None	NR	Very low[d]	The evidence is very uncertain regarding whether nivolumab increases risk of

Outcome Measure	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)		Difference	Certainty	What happens
			Nivolumab	Placebo			
							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 1000	None	NR	Very low[d]	The evidence is very uncertain regarding whether nivolumab increases risk of diabetes mellitus when compared to placebo
Arthritis Follow-up: within 100 days of last dose	790 (1 RCT)	NR	25 per 1000	4 per 1000	NR	Very low[d]	The evidence is very uncertain regarding whether nivolumab increases risk of arthritis when compared to 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
[a]Could not be rated because no effect estimates were available for this time point
[b]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 risk of bias due to large difference in treatment discontinuations between groups
[c]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 risk of bias due to large difference in treatment discontinuations between groups
[d]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 risk of bias due to large difference 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 an NMA and a Bucher method ITC in patients with non-metastatic 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, multicenter population.

Efficacy Results

For Checkmate-76K, data informing 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 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 ≥ 3 AE incidence (OR [95% CI] 1.09 [0.41, 2.94]) or treatment-related any-grade AE incidence (1.55 [0.99, 2.43]) between nivolumab and pembrolizumab.

Critical Appraisal

The sponsor conducted an NMA used 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 two 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. Results beyond 23 months would therefore be less reliable and subject to increasingly greater extrapolation as time points become longer. In addition, the differential follow up times for the studies exacerbates the uncertainty in the comparisons for later timepoints 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 that this was a reasonable assumption.

To align definitions of recurrence between these two 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.

There were no significant differences observed between nivolumab and pembrolizumab for RFS.

There were no significant differences observed between nivolumab and pembrolizumab for treatment-related AEs (any grade, grade ≥ 3). The sponsor stated that all cause AEs were an outcome of interest, but no analyses of this outcome was 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 harms outcomes for nivolumab compared to pembrolizumab in patients with non-metastatic resected stage IIB/C cutaneous melanoma.

Economic Evidence

Cost and Cost-Effectiveness

Table 3: 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.[a]
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.
Key limitations	• 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. • Confidential pricing agreements exist for pembrolizumab for this indication and nivolumab for another melanoma indication.
CADTH reanalysis results	CADTH did not undertake a base case reanalysis. Based on the public list prices, nivolumab remains cost saving compared with pembrolizumab. CADTH could not address the existence of confidential pricing for both products. If nivolumab is considered similar to pembrolizumab in terms of efficacy and safety, the extent of savings that will be realized with the use of nivolumab compared to pembrolizumab is dependent on patient weight.

[a] 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-participating 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 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 in the extent to which nivolumab will displace pembrolizumab and the price paid by public plans for pembrolizumab remains.

pERC Information

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Meeting date: April 10, 2024

Regrets:

None

Conflicts of interest:

None