Canadian Journal of Health Technologies
February 2024 Volume 4 Issue 2

CADTH Reimbursement Recommendation

Nivolumab and Relatlimab (Opdualag)

Indication: For the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma

Sponsor: Bristol Myers Squibb Canada

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Opdualag?

CADTH recommends that Opdualag be reimbursed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma if certain conditions are met.

Which Patients Are Eligible for Coverage?

Opdualag should only be covered to treat patients aged 12 years or older who have a histologically confirmed diagnosis of unresectable stage III or stage IV (metastatic) melanoma and have not received prior systemic therapy for advanced melanoma. Patients should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Patients who had prior adjuvant or neoadjuvant anti–programmed death-1 (PD-1) or anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) therapy if the therapy was completed at least 6 months before the date of recurrence are eligible for reimbursement. Opdualag should not be reimbursed in patients with active brain metastases, uveal melanoma, and active autoimmune disease. Opdualag should only be reimbursed if the price of Opdualag is reduced. The feasibility of adoption of Opdualag must also be addressed.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial (RELATIVITY-047) demonstrated that treatment with Opdualag when compared with nivolumab monotherapy resulted in added clinical benefit in patients with previously untreated, histologically confirmed, unresectable stage III or stage IV (metastatic) melanoma.
- Opdualag met some of the identified patient needs, such as an additional treatment option that is effective in terms reducing the risk of cancer growing, spreading, or getting worse (progression-free survival) and has manageable adverse events.
- CADTH's assessment of the health economic analysis found that there was insufficient evidence to justify a price premium for Opdualag over nivolumab and ipilimumab combination therapy. The total drug cost of Opdualag therefore should not exceed the total drug cost of nivolumab and ipilimumab.

Summary

- Based on the sponsor's submitted price and public list prices for the comparators, the 3-year budget impact of Opdualag is estimated to be $34,304,588.

Additional Information

What Is Melanoma?

Melanoma is a cancer that occurs in skin cells that produce melanin. Melanoma that cannot be removed by surgery (unresectable) or that has spread to other parts of the body (metastatic disease) is associated with a low survival rate.

Unmet Needs in Melanoma

Current treatments may be associated with a number of side effects that may lead to treatment interruptions, delays, or discontinuation. There is an unmet medical need for an additional novel immune checkpoint inhibitor combination therapy in metastatic melanoma which can be used regardless of *BRAF* mutation status. The novel therapy should offer increased efficacy in relation to anti–PD-1 monotherapy and should have a favourable safety profile that does not result in additive toxicities as seen with conventional dual immunotherapy combinations.

How Much Does Opdualag Cost?

Based on the CADTH base case, the budget impact from the introduction of Opdualag is expected to be $4,734,946 in year 1, $12,890,614 in year 2, and $16,679,027 in year 3. The 3-year net budget impact was estimated to be $34,304,588.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that nivolumab-relatlimab be reimbursed for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase II/III, double-blinded, randomized, active controlled and ongoing trial (RELATIVITY-047) demonstrated that treatment with nivolumab-relatlimab fixed-dose combination (FDC), when compared with nivolumab monotherapy, resulted in added clinical benefit in patients with previously untreated, histologically confirmed, unresectable stage III or stage IV (metastatic) melanoma. Nivolumab-relatlimab was associated with a statistically significant and clinically important increase in progression-free survival (PFS) benefit when compared with nivolumab monotherapy (primary analysis: median follow-up = 13.2 months; hazard ratio [HR] = 0.75; 95% confidence interval [CI], 0.62 to 0.92; P = 0.0055). Nivolumab-relatlimab may result in a clinically important increase in overall survival (OS) when compared with nivolumab monotherapy (HR = 0.80; 95% CI, 0.64 to 1.01; P = 0.0593). However, there remains uncertainty in the OS results due to the inadequate length of follow-up for this outcome and the 95% CI included no difference between nivolumab-relatlimab and nivolumab monotherapy. Based on descriptive final analyses, a total of 10.3% (95% CI, 3.4% to 17.3%) more patients in the nivolumab-relatlimab group achieved an objective response compared with the nivolumab group after a median follow-up of 19.3 months. After a median follow-up of 19.3 months, health-related quality of life (HRQoL) (Functional Assessment of Cancer Therapy-Melanoma [FACT-M], 3-Level EQ-5D [EQ-5D-3L] utility index scores, and EQ-5D visual analogue scale [VAS]) in the nivolumab-relatlimab group and nivolumab group remained generally stable (no clinical meaningful improvement or deterioration) during the treatment period. There were little to no differences between nivolumab-relatlimab and nivolumab monotherapy in FACT-M, EQ-5D-3L utility index scores, and EQ-5D-VAS.

Despite the available treatment options, there remains an unmet therapeutic need for effective treatment options for patients with unresectable or metastatic melanoma. Patient groups indicated that there is an ongoing need for better options with fewer adverse events (AEs) and longer responses as well as the need to have available treatment options when 1 therapy does not work or stops working. Nivolumab-relatlimab compared to nivolumab monotherapy was effective with respect to PFS. Although there were numerically more patients who experienced AEs (e.g., grade 3 or 4 AEs) in the nivolumab-relatlimab group than in the nivolumab monotherapy group, the AEs were generally manageable.

At the sponsor-submitted price for nivolumab-relatlimab and publicly listed prices for immunotherapies considered in the submitted indirect treatment comparison (nivolumab-ipilimumab combination, pembrolizumab, ipilimumab, and nivolumab monotherapy) nivolumab-relatlimab was more costly than nivolumab-ipilimumab combination, pembrolizumab, ipilimumab, and nivolumab monotherapy. Because there was insufficient evidence to conclude that nivolumab-relatlimab is as effective or better than

nivolumab-ipilimumab combination to justify a cost premium, the total drug cost of nivolumab-relatlimab should not exceed the total drug cost of nivolumab-ipilimumab combination.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nivolumab-relatlimab FDC should be reimbursed only in patients with all of the following characteristics: 1.1. histologically confirmed unresectable stage III or stage IV (metastatic) melanoma 1.2. have not received prior systemic therapy for unresectable or metastatic melanoma 1.3. aged 12 years or older 1.4. good performance status.	Evidence from the RELATIVITY-047 study demonstrated that treatment with nivolumab-relatlimab FDC when compared with nivolumab monotherapy resulted in added clinical benefit in patients with previously untreated, histologically confirmed, unresectable stage III or stage IV (metastatic) melanoma. These conditions are reflective of the patients enrolled in the RELATIVITY-047 study.	—
2. Treatment with nivolumab-relatlimab FDC could be reimbursed in patients who had prior adjuvant or neoadjuvant anti–PD-1 or anti–CTLA-4 therapy if the therapy was completed at least 6 months before the date of recurrence.	As per eligibility criteria for RELATIVITY-47, prior adjuvant or neoadjuvant anti–PD-1 or anti–CTLA-4 therapy was allowed if all related AEs had returned to baseline or stabilized, provided that prior adjuvant or neoadjuvant anti–PD-1 or anti–CTLA-4 therapy was completed at least 6 months before the date of recurrence.	—
3. Treatment with the nivolumab-relatlimab FDC should not be reimbursed in patients with: 3.1. active brain metastases 3.2. uveal melanoma 3.3. active autoimmune disease.	Patients with these conditions were excluded from the RELATIVITY-047 trial. As a result, there was no evidence reviewed for patients with active brain metastases, uveal melanoma, and active autoimmune disease.	—
Renewal		
4. Treatment with nivolumab-relatlimab FDC may continue unless any of the following occurs: 4.1. clinical or radiographic disease progression 4.2. intolerable side effects that cannot be managed by dose interruption.	These conditions are reflective of the intervention and discontinuation criteria in the RELATIVITY-047 trial and/or the clinical experts' input.	—
5. Patients should be assessed for a response to treatment with nivolumab-relatlimab FDC every 2 to 3 months initially and then as per standard of care.	In the RELATIVITY-047 trial, tumour assessments began 12 weeks from randomization and continued every 8 weeks up to week 52, and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurred later.	—

Reimbursement condition	Reason	Implementation guidance
	According to clinical experts, initial response assessments are at 3-month intervals and, as the patient responds, the response assessment can be tailored with increased intervals over time.	
Discontinuation		
6. Treatment with nivolumab-relatlimab FDC should be discontinued upon the occurrence of any of the following: 6.1. clinical or radiographic disease progression 6.2. unacceptable toxicity.	These conditions are reflective of the intervention and discontinuation criteria in the RELATIVITY-047 trial as well as the clinical experts' input.	—
Prescribing		
7. Nivolumab-relatlimab FDC should only be prescribed by clinicians who: 7.1. have expertise in diagnosis and management of patients with melanoma 7.2. are familiar with the toxicity profile associated with nivolumab-relatlimab FDC.	To ensure that the nivolumab-relatlimab FDC is prescribed only for appropriate patients and that patients receive optimal care for toxicity management.	—
Pricing		
8. A reduction in price	Given the uncertainty in the relative efficacy of nivolumab-relatlimab compared to nivolumab-ipilimumab, the total drug cost of nivolumab-relatlimab should not exceed the total drug cost of nivolumab-ipilimumab. Given the potential that nivolumab-relatlimab would not be considered equally efficacious to nivolumab-ipilimumab, a further price reduction to achieve cost savings may be warranted.	—
9. The feasibility of adoption of nivolumab-relatlimab must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).	—

AE = adverse event; BICR = blinded independent central review; CTLA-4 = cytotoxic T-lymphocyte–associated antigen 4; FDC = fixed-dose combination; PD-L1 = programmed death-ligand 1.

Discussion Points

- pERC discussed the current treatment options available to patients and noted that treatment is dependent on *BRAF* mutation status. First-line treatment options include immune checkpoint inhibitor (ICI) monotherapy (pembrolizumab, nivolumab, ipilimumab), ICI combination therapy (nivolumab-ipilimumab), and targeted BRAF therapy. Current standard first-line therapy for patients with

BRAF-negative melanoma who are fit is nivolumab combined with ipilimumab; for those who are less fit, single-drug pembrolizumab or nivolumab. For *BRAF* mutation–positive melanoma, patients can either receive the ICI combination first or BRAF-directed therapy; those who are less fit have access to single-drug nivolumab or pembrolizumab. pERC acknowledged the input from the clinical experts that suggests nivolumab-ipilimumab is the preferred standard of care in the first-line setting for patients who are young and healthy and willing to tolerate the AEs associated with treatment, irrespective of *BRAF* mutation status.

- pERC discussed the possible place in therapy of nivolumab-relatlimab and concluded that nivolumab-relatlimab would be another alternative treatment option for patients who are not fit enough to receive nivolumab-ipilimumab combination or for patients who are ineligible for ipilimumab and would otherwise receive nivolumab monotherapy, pembrolizumab monotherapy, or targeted BRAF therapy.
- Based on the direct evidence, although pERC was confident in the PFS benefit of nivolumab-relatlimab compared to nivolumab monotherapy, pERC was less confident in the OS benefit because these results were not statistically significant and longer length of follow-up is needed to confirm an OS benefit.
- pERC acknowledged an established clinical benefit with nivolumab-ipilimumab combination for patients who are fit enough to endure the toxicities associated with this combination compared with nivolumab. Although the RELATIVITY-047 study compared nivolumab-relatlimab to nivolumab monotherapy, there is no direct evidence to suggest a clinical benefit compared to nivolumab-ipilimumab combination. There remains uncertainty in the comparative efficacy of nivolumab-relatlimab compared to relevant comparators, including nivolumab-ipilimumab. However, pERC acknowledged that, according to clinical expert opinion, nivolumab-relatlimab has less toxicity than nivolumab-ipilimumab.
- Although the sponsor submitted ITCs to address this gap, the evidence from these comparisons was inconclusive due to inherent limitations (between trial differences, immature OS data, important outcomes such as overall response rate [ORR] and time to progression were not included). As a result, there is insufficient evidence to support a conclusion that nivolumab-relatlimab provides additional or similar benefit to that provided by nivolumab-ipilimumab. Consequently, pERC concluded that the evidence may support the conclusion that the total drug cost of nivolumab-relatlimab should be lower than the total drug cost of nivolumab-ipilimumab.
- pERC discussed the uncertainty present in the budget impact analysis. pERC recognized that the choice of first-line therapy will be determined by patient preference, fitness, willingness to endure toxicity, and discussions between clinician and patient, which is consistent with clinical expert opinion. Clinical experts suggested that given the number of efficacious treatments available for melanoma in the unresectable, metastatic setting, it was difficult to estimate the likely change in prescribing patterns that might result if nivolumab-relatlimab were reimbursed. The reimbursement of first-line nivolumab-relatlimab is also likely to have implications on prescribing patterns for second-line therapies that are difficult to predict. This uncertainty in the market share of different treatments

(and therefore the overall assessment of budget impact) may present challenges for the feasibility of adoption for this reimbursement recommendation.

Background

Melanoma is a neoplasm originating from melanocytes or the pigment-producing cells of the skin. The clinical symptoms of advanced melanoma include swollen lymph nodes, hard lump on the skin, unexplained pain, feeling very tired or unwell, and unexplained weight loss. The mean age at diagnosis of advanced metastatic melanoma is approximately 59 years in Canada. The diagnosis of melanoma is based on skin examination, physical examination, skin and/or lymph node biopsy, and diagnostic imaging (i.e., CT). According to the Canadian Cancer Society, 10.4% of all new melanomas are stage III at diagnosis and 3.9% are stage IV (i.e., metastatic disease). Poor prognostic factors include Eastern Cooperative Oncology Group (ECOG) performance status of 2 or higher, elevated lactate dehydrogenase, nodal involvement and metastases, increased tumour thickness, ulceration, and mitoses at least 1 per mm^2 in thin T1 melanomas. Approximately 70% of metastatic melanomas have mutually exclusive mutations in B-Raf proto-oncogene (BRAF), neuroblastoma RAS viral oncogene homologue (*NRAS*) gene , c-KIT, and *GNAQ* or *GNA11*, which activate the mitogen-activated protein kinase pathway leading to promotion of cell proliferation, prevention of apoptosis, and angiogenesis.

Approximately 38% to 51% of patients with stage III or IV melanoma have a mutation in the *BRAF* gene. An Australian study of patients with advanced melanoma reported a similar rate, with 48% of tumours being *BRAF* V600 mutation positive. In Canada, melanoma accounted for 3.8% of new cancer cases and 1.5% of cancer deaths in 2021. An estimated 9,000 people were diagnosed with melanoma in 2022 in Canada, with an age-standardized incidence rate of 23.5 per 100,000 in 2018 (excluding Quebec) based on data from Statistics Canada. Incidence is slightly higher in men than in women (25.9 per 100,000 versus 21.2 per 100,000). An estimated 1,200 persons died from melanoma in 2022 in Canada, with an age-standardized mortality rate of 2.7 per 100,000. In Canada, stage IV distant metastatic disease is associated with a 5-year survival rate of 18%. However, consistent with the observed decline in mortality rates, melanoma survival rates have improved in recent years with the introduction of novel immunotherapies and BRAF-targeted therapies with BRAF and MEK inhibitors.

Important treatment goals of systemic therapy in metastatic advanced melanoma include prolonging survival, generating durable responses, providing symptom relief, minimizing treatment toxicities, and maintaining quality of life. According to the clinical experts CADTH consulted for this review, immunotherapy is the first line of choice for melanoma regardless of *BRAF* status. The ICI immunotherapies routinely used for the first-line treatment of metastatic melanoma in Canada include nivolumab-ipilimumab combination therapy, nivolumab (anti–programmed death [PD]-1) monotherapy, ipilimumab (anti–cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]) monotherapy, and pembrolizumab (anti–PD-1) monotherapy. However, the use of nivolumab-ipilimumab has been increasing. According to the clinical experts CADTH consulted for this review, nivolumab-ipilimumab is the first line of choice among the ICIs. After the first line, the treatment decisions are largely determined by *BRAF* mutation status. Patients with no *BRAF* mutation

are treated with immunotherapies, and patients with *BRAF* mutations are eligible for treatment with targeted therapies. Targeted-therapy regimens that have been approved by Health Canada and are recommended for reimbursement by pERC include encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor), vemurafenib (BRAF inhibitor) plus cobimetinib (MEK inhibitor), and dabrafenib (BRAF inhibitor) plus trametinib (MEK inhibitor). The clinical experts CADTH consulted for this review indicated that targeted therapy use as monotherapy is negligible and not reflective of clinical practice in Canada. It was reported that patients with advanced melanoma rarely receive targeted therapy as a single drug (< 5%). According to the clinical experts CADTH consulted for this review, there is an unmet medical need for an additional novel ICI combination therapy in metastatic melanoma that can be used regardless of *BRAF* mutation status. The novel therapy should offer increased efficacy in relation to anti–PD-1 monotherapy and should have a favourable safety profile that does not result in additive toxicities as seen with conventional dual immunotherapy combinations — a combination treatment regimen involving an ICI combined with a drug with a different mechanism of action.

Nivolumab is a humanized IgG4 monoclonal antibody ICI that binds to the PD-1 receptor and blocks its interaction with programmed death-ligand 1 (PD-L1) and ligand 2 (PD-L2), releasing PD-1 pathway–mediated inhibition of the immune response, including the antitumour immune response. Relatlimab is a novel, first-in-class ICI that targets the lymphocyte-activation gene 3 (LAG-3) receptor. Relatlimab is a humanized IgG4 monoclonal antibody that binds to the LAG-3 receptor and prevents LAG-3–mediated inhibition of the immune response by blocking its interaction with ligands, ultimately leading to an antitumour response. LAG-3 and PD-1 are 2 distinct inhibitory immune checkpoint pathways, often co-expressed on tumour-infiltrating lymphocytes. They act synergistically on effector T cells, leading to the development of T-cell exhaustion and impaired cytotoxic function. The recommended dose of nivolumab-relatlimab for adult patients is 480 mg nivolumab and 160 mg relatlimab every 4 weeks.

The recommended nivolumab-relatlimab dosage for pediatric patients who are at least 12 years old and weigh at least 40 kg is the same as for adults. A recommended dose has not been established for pediatric patients who are 12 years or older and weigh less than 40 kg. Nivolumab-relatlimab is supplied as concentrate for solution for infusion: 240 mg of nivolumab per 20 mL (12 mg/mL) and 80 mg of relatlimab per 20 mL (4 mg/mL) in a single-dose vial (FDC).

The Health Canada–approved indication of interest for this review is nivolumab-relatlimab FDC for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma. The CADTH reimbursement request aligns with this Health Canada indication. The nivolumab-relatlimab FDC was reviewed by Health Canada through the Standard Review Pathway. It has not been reviewed previously by CADTH.

Sources of Information Used by the Committee

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

- a review of 1 phase II/III, double-blinded, randomized controlled and ongoing trial (RELATIVITY-047, N = 714) in patients with previously untreated, unresectable, or metastatic melanoma
- patient perspectives gathered by 2 patient groups, Melanoma Canada and Save Your Skin Foundation (SYSF)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with melanoma
- input from 1 clinician group, Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees)
- a review of the pharmacoeconomic model and report and indirect treatment comparisons submitted by the sponsor.

Stakeholder Perspectives

Patient Input

CADTH received 2 patient group submissions from Melanoma Canada and SYSF. Data were gathered by Melanoma Canada via an online survey. A total of 119 individual patient responses combined with 84 caregiver responses were received; 35 patient respondents indicated they had no caregiver. Of the total responses for patients, 81 were female and 38 were male. There were 26 patients that had stage 0 melanoma, 17 had stage I, 10 had stage II, 18 had stage III, and 29 had stage IV; 19 patients did not know their stage. Two patients in this survey were treated with nivolumab-relatlimab FDC.

Information was obtained by SYSF through online surveys, virtual patient roundtables and one-on-one conversations, which included 60 patients with melanoma of 12 patients on the drug under review (nivolumab-relatlimab) and was gathered over the past 6 months. There were 37 females and 23 males aged between 18 and 89 years. A total of 18 (out of 60) respondents were from outside of Canada (the US, Australia, France).

Most patients reported that pain, scarring, lymphedema, fatigue, anxiety, fear, and depression are common impacts of the disease that affect the quality of life for patients and their families. Caregivers reported that the biggest impact on them of dealing with the diagnosis is the mental stress, the negative financial impact to the family with the loss of income from a working partner, and the additional responsibilities that they have to perform for the home and family and caring for their loved one. Some respondents explained the impact of melanoma using the following terms: scared, disbelief, unsettled, anxious, teary, disrupted life, and totally life changing.

In terms of current therapy options, based on 119 of the respondents from Melanoma Canada's survey, 55% of respondents had been treated with some form of drug therapy. There were 9 patients who were treated with multiple therapies. A total of 92% of patients treated with available drug therapies indicated that they felt the side effects were worth it for the anticipated results. Moreover, approximately 20% of patients experienced issues in accessing treatment. SYSF's survey results also mentioned the same issues because patients in remote areas of Canada have problems getting to treatment if needed, the travel costs and time off from work put extra stress on patients and caregivers, there are huge expenses and increased stress to themselves and their family, and there is also concern about being treated far from home and their support system. There was very little access to the drug under review (Ontario and Quebec only). There were a number of patients in Canada who could not get access to the drug under review, which might have been their only option.

Regarding the improved outcomes, both patient groups identified that there is a vast opportunity for improvement with a wider variety of more effective treatment options with minimal side effects and a longer response being made available.

There were 2 respondents from Melanoma Canada's survey and 12 respondents from SYSF's survey who indicated that they had experience with the drug under review with the primary method of access to the drug under review through a clinical trial. There were 12 respondents who explained that the benefits outweighed the experience of side effects, primarily rash and fatigue, which were somewhat manageable.

Melanoma Canada believes that there is an ongoing need for better options and options for when 1 therapy does not work or stops working. Melanoma Canada also noted that melanoma is very difficult to treat once it has spread. Effective treatments, biomarkers, and earlier stage treatments are needed to prevent some of the quality-of-life impacts from surgery, loss of income, duration of illness, and the impact on mental health for the patient and caregiver. According to Melanoma Canada, the drug under review is another improvement and option for a cancer that continues to be on the rise and is complex to treat.

Clinician Input

The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of adult and pediatric patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma.

The clinical experts indicated that the goal is to increase OS rates, to slow down progression, improve symptoms, improve quality and quantity of life, and to minimize toxicity, especially long-term significant toxicities. The clinical experts indicated that formulations are needed to improve convenience. Currently the standard of care for metastatic melanoma in Ontario is nivolumab-ipilimumab if the patient is able to tolerate the drugs relating to potential toxicities. Failure to respond to nivolumab-ipilimumab leads to potentially switching to *BRAF* inhibitor plus *MEK* inhibitor in patients who are *BRAF* positive. Pembrolizumab may be attempted as monotherapy or nivolumab as monotherapy if a patient experiences too many AEs due to nivolumab-ipilimumab combination treatment. The clinical experts indicated that immunotherapy is not 100% effective. The response rates of combination nivolumab-ipilimumab is approximately 56%.

Patients may initially get a response and then progress eventually. After progression, new treatments are needed. Moreover, sometimes treatments are effective, but the AEs are not tolerable and treatment has to be aborted despite efficacy so less toxic treatments that are more tolerable and less dangerous are needed. This is an unmet need. According to the clinical experts, there is no real beneficial second-line therapy better than nivolumab-ipilimumab right now. New therapy is needed to increase response rates with fewer AEs. Furthermore, current standard practice, according to the clinical experts, would be to discuss dual drugs versus single-drug immunotherapy if there are no contraindications with the patient. Factors that would be considered in determining the most suitable treatment include patient goals, age, comorbidities, bulk of disease, sites of disease, and pace of disease. If the patient elected dual-drug therapy, they may de-escalate to a single drug for toxicity management. If the patient progresses on dual therapy and has a *BRAF* mutation, *BRAF* or *MEK* inhibitors would be offered. According to the clinical expert, dual immunotherapy has been recognized as a potentially curable regimen. In addition, many trials are based on fixed dosing and limited vial sizes. The clinical experts noted that many provinces reimburse these therapies based on weight and that clinics are challenged to cohort patients to minimize drug wastage.

One clinical expert indicated that given its equivalency to nivolumab-ipilimumab and fewer toxicities, they consider the new treatment (nivolumab-relatlimab FDC) under review as a first-line treatment for patients. The clinical experts highlighted that fewer AEs may mean more patient compliance thus better outcomes overall. Less toxicity may mean fewer hospital admissions which is better for patients overall and more economically sound and would offset the extra cost of the drug. Nivolumab-relatlimab FDC could also be an alternative to nivolumab-ipilimumab, which is currently first line in Ontario. The other clinical expert indicated that if this regimen is approved, then the options would be discussed with patients, nivolumab-ipilimumab versus nivolumab-relatlimab FDC, regarding OS, PFS, and toxicities. The clinical expert also noted that nivolumab-relatlimab FDC is directly compared to nivolumab monotherapy in the RELATIVITY-047 trial; nivolumab-relatlimab FDC is the first class drug; nivolumab-relatlimab FDC may be used as first line or second line of ICIs; nivolumab-relatlimab FDC would not be reserved for those patients who are intolerant, but rather would benefit from an effective regimen with less toxicities; nivolumab-relatlimab FDC is expected to cause a shift in treatment paradigms; those receiving candidates for single-drug immunotherapy would be offered nivolumab-relatlimab FDC; and those candidates considered for ipilimumab plus nivolumab may be offered or choose nivolumab-relatlimab FDC. The clinical expert stated that this nivolumab-relatlimab FDC regimen may replace nivolumab-ipilimumab for less robust patients.

The clinical experts indicated that all patients with metastases can be offered this treatment because it was beneficial regardless of *BRAF* status, PDL-1 and LAG-3 percentage, or stage. It is similar to other immunotherapy combinations and thus could be offered to all patients. In addition, the experts also stated that it will be important to follow OS data as it matures, to know the efficacy in brain metastases, and to know if the combination decreases or delays the occurrence of brain metastases.

Regarding response assessment, the clinical experts indicated that it is needed to assess response for improved patient symptoms and the modified immunotherapy RECIST criteria because there can be pseudoprogression in the beginning of treatment. Usually, it can take up to 2 to 3 months to evaluate a true response. At the beginning, response is assessed at 3-month intervals. As patients respond, the response

assessment can be tailored and increased to every 6 months. Improved survival is the goal. The clinical experts noted that the clinical outcomes assessments are aligned with the clinical trial outcomes; physicians and patients review toxicities, symptom control, and objective evidence of disease response in an ongoing fashion during active treatment.

Regarding discontinuation, the clinical experts indicated the nivolumab-relatlimab FDC should be discontinued when obvious disease progression on imaging occurs with no improvement in symptoms. According to the clinical experts, when harmful grade 3 to 4 AEs occur, patients should at least pause the treatment and start to treat the AE then determine if the treatment can be restarted at a lower dose.

The clinical expert noted that treatments for metastatic melanoma should be provided by specialist medical oncologists and pharmacists in a Canadian cancer centre or, if at a community centre, then supervised or somehow connected to a cancer centre and experts for advice. According to the clinical expert, a centre administering or managing patients on nivolumab-ipilimumab are well equipped to manage this regimen.

Clinician Group Input

CADTH received 1 clinician group submission from the OH-CCO Skin Cancer Drug Advisory Committee. Of note, at the time of OH-CCO's input, the proposed Health Canada indication was not line specific (i.e., indicated for the treatment of adult and pediatric patients [12 years and older and weighing at least 40 kg] with unresectable or metastatic melanoma); however, after the clinician group input was received, the indication was approved to first line (i.e., for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma who have not received prior systemic therapy for unresectable or metastatic melanoma). In the first-line metastatic or unresectable setting, the current treatments can include single-drug nivolumab or pembrolizumab, nivolumab-ipilimumab combination, and BRAF-targeted agents (for patients with *BRAF* mutations). The BRAF-targeted therapy options are dabrafenib-trametinib, cobimetinib-vemurafenib, and binimetinib-encorafenib. If patients received pembrolizumab or nivolumab in first line, the subsequent line options are ipilimumab alone or BRAF-targeted therapy (for patients with *BRAF* mutation). If nivolumab-ipilimumab followed by nivolumab maintenance is used in first line, only patients with a *BRAF* mutation have a second-line option to use BRAF-targeted therapy. Patients who received first-line BRAF-targeted therapy may be eligible for pembrolizumab, nivolumab, or nivolumab-ipilimumab in the second-line setting. If treated with pembrolizumab or nivolumab, the patient may be eligible to use ipilimumab further downstream.

According to OH-CCO's Drug Advisory Committees, the drug under review has a higher response rate than single-drug nivolumab in patients with unresectable or metastatic melanoma as per the RELATIVITY 047 trial. Although there is no head-to-head comparison trial, this combination also has less toxicity than nivolumab-ipilimumab (the treatment-related AEs are reported in the CHECKMATE 067 trial), which might fill some of the unmet needs of the standard treatment.

OH-CCO's Drug Advisory Committees reported that patients who are not able to tolerate nivolumab-ipilimumab or who would be treated with single-drug PD-1 inhibitor would be suitable for receiving drug under review in the first-line metastatic or unresectable setting.

OH-CCO's Drug Advisory Committees believed that a clinically meaningful response would be improved survival, reduction in the frequency or severity of symptoms, attainment of major motor milestones, ability to perform activities of daily living, improvement of symptoms, and stabilization (no deterioration) of symptoms. Treatment response will be routinely assessed clinically, and by CT and/or PET scans approximately every 3 months.

OH-CCO's Drug Advisory Committees mentioned that the most likely reason to discontinue treatment would be confirmed disease progression and/or unmanageable toxicities.

OH-CCO's Drug Advisory Committees noted that the drug under review should be administered in an outpatient cancer clinic, prescribed by a medical oncologist.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's Reimbursement Review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 2.

Table 2: Summary of Drug Plan Input and pERC Response

Drug program implementation questions	pERC response
Relevant comparators	
Issues with the choice of comparator in the submitted trial(s) The comparator in RELATIVITY-047 was single-drug nivolumab, which is publicly funded in Canada. Nivolumab-relatlimab is proposed as an alternative to currently available PD-1 inhibitors for unresectable or metastatic melanoma. Pembrolizumab and nivolumab are both publicly funded.	Comment from the drug programs to inform pERC deliberations.
Other implementation issues regarding relevant comparators (e.g., access and funding, covered population) Other therapies funded in Canada are potential comparators in unresectable or metastatic melanoma. These were not included as comparators in RELATIVITY-047: • ipilimumab-nivolumab • pembrolizumab • dabrafenib-trametinib • cobimetinib-vemurafenib • binimetinib-encorafenib	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Disease diagnosis, scoring, or staging for eligibility RELATIVITY-047 required PD-L1 and LAG-3 testing in all patients. Patients with expression or no expression were included. The study found that response was not predicted by	pERC noted that the results from RELATIVITY-047 did not show any difference in the subgroups responses for PD-L1 and LAG-3. The PFS benefit observed was irrespective of PD-L1 and LAG-3 status. As a result, pERC agreed with the clinical experts that

Drug program implementation questions	pERC response
expression of these markers. Should PD-L1 and LAG-3 testing be done routinely in this population?	there is no need in practice for routine PD-L1 and LAG-3 testing to select patients for this therapy.
What is the current status of access to LAG-3 testing in jurisdictions across Canada?	pERC acknowledged the clinical experts' response that LAG-3 testing is not routinely done in jurisdictions across Canada.
What is the turnaround time for testing?	pERC noted the input received from the clinical experts which stated that most tests take 2 weeks; however, turnaround time for testing depends on if it is next-generation sequencing or immunohistochemistry.
Is LAG-3 testing standardized?	pERC acknowledged the clinical experts' input which recognized that LAG-3 testing is not routinely done.
Other patient characteristics for eligibility (e.g., age restrictions, comorbidities) The trial was in patients 12 years and older and more than 40 kg. Should patients younger than 12 years and less than 40 kg be considered?	Patients younger than 12 years or who weigh less than 40 kg would not be considered. pERC noted that the Health Canada indication does not include children younger than 12 years. The safety and efficacy of nivolumab-relatlimab FDC have not been established in pediatric patients younger than 12 years or in patients 12 years or older who weigh less than 40 kg; this is outlined in the Health Canada product monograph.
Patients with active, known, or suspected autoimmune disease were excluded (exceptions: type 1 diabetes mellitus, hypothyroidism on hormone replacement, skin disorders). Should patients with autoimmune disorders be considered at the discretion of the treating physician?	pERC agreed with the clinical experts that patients with autoimmune disorders, at the discretion of the treating physician, would be considered provided that their disease is not active. Hence, patients with active autoimmune disorders would not be eligible for reimbursement.
Prior therapies required for eligibility There are no other LAG-3 inhibitors currently available in Canada. Should the enrolment criteria regarding prior neoadjuvant or adjuvant treatment used in RELATIVITY-047 be used?	pERC recognized that nivolumab-relatlimab would be an alternative therapy in patients who progress on BRAF or MEK therapies used in the adjuvant setting. Although pERC noted that the enrolment criteria permitted neoadjuvant or adjuvant IFN therapy with the last dose at least 6 weeks before randomization, pERC noted the infrequent and rare use of IFN therapy in neoadjuvant or adjuvant in Canada. Prior adjuvant or neoadjuvant anti–PD-1 or anti–CTLA-4 therapy should be followed as per RELATIVITY-047.
Should patients with potentially resectable disease be eligible?	pERC concluded that patients who are not currently resectable would be eligible.
Patients enrolled had previously untreated unresectable or metastatic melanoma. Currently, per CADTH's provisional funding algorithm, single-drug PD1 inhibitors are funded in first line or second line after BRAF-targeted therapy. Are there data to support the use of nivolumab-relatlimab in the second line after BRAF-targeted therapy?	pERC noted that this question is out of scope for this review as the nivolumab-relatlimab is indicated for first-line use only.
Eligibility for re-treatment Should re-initiation of treatment be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment?	pERC agreed with the clinical experts that re-initiation of treatment would be permitted for those who chose to take a treatment break but did not experience progression or unacceptable toxicity while on treatment on a case-by-case basis based on the discretion of the treating clinician.

Drug program implementation questions	pERC response
Should re-initiation be considered in the case of progression while off therapy? After a defined treatment break duration?	pERC acknowledged that, commonly, progression after a 6-month break is accepted as a guideline to reinstitute treatment. However, pERC agreed with the clinical experts that re-initiation may be considered regardless of the disease-free interval provided the disease progression occurred while off therapy.
Special subtypes (not explicitly mentioned in the indication) to consider separately for eligibility Patients with active CNS disease were excluded. Should they be eligible? Patients with uveal melanoma were excluded. Should they be eligible?	pERC considered the input from the clinical experts and concluded that patients with active CNS disease and patients with uveal melanoma would not be eligible for nivolumab-relatlimab.
Considerations for discontinuation of therapy	
Definition of loss of response, absence of clinical benefit, or disease progression In RELATIVITY-047, treatment was continued until progression or unacceptable toxicity. What is the most appropriate definition for progression?	According to the clinical experts, progression is based on the RECIST criteria immunotherapy subset RECIST 1.1 criteria. The clinical experts also acknowledged that there is some pseudoprogression with immunotherapy.
Patients could also continue treatment beyond progression if demonstrating a clinical benefit. Is this appropriate in any scenario other than pseudoprogression?	pERC considered the input from the clinical experts and concluded that progression should be left up to the treating physician to determine. pERC does not recommend continuing the therapy in those with confirmed progression.
Treatment interruptions If treatment is interrupted, can it be resumed? Is there a specific time frame?	pERC agreed with the clinical experts that if treatment is interrupted, it can be resumed. The time frame is after toxicity is resolved as long as it was not a life-threatening toxicity.
Can treatment be resumed after holding for a toxicity that resolves to acceptable levels?	Yes, treatment can be resumed after holding for a toxicity that resolves to acceptable levels.
Considerations for prescribing of therapy	
Dosing, schedule or frequency, and dose intensity The fixed-dose combination of 160 mg of relatlimab and 480 mg of nivolumab is given every 4 weeks. Is there potential for any other dosing options? Weight based?	Nivolumab-relatlimab FDC was manufactured as fixed dose, according to the clinical experts, so weight-based adjusted remuneration should not be based on weight dosing.
Generalizability	
Populations of interest matching the indication but with insufficient data Patients with ECOG > 1 were excluded from the trial. Should they be eligible for treatment?	pERC concluded that patients with good performance status should be eligible for treatment, and the decision to treat a patient with performance status of 2 or higher should be up to the treating physician.
Populations outside the indication or reimbursement request but of interest to jurisdictions Should any patients considered appropriate for treatment with combination nivolumab-ipilimumab be considered for nivolumab-relatlimab?	pERC noted the input from the clinical experts which stated if nivolumab-relatlimab is approved for reimbursement, then both options (nivolumab-ipilimumab and nivolumab-relatlimab) could be considered for patients.

Drug program implementation questions	pERC response
Is there any evidence or clinical rationale to choose nivolumab-relatlimab over nivolumab-ipilimumab?	pERC discussed that there is no direct evidence comparing nivolumab-relatlimab to nivolumab-ipilimumab, and although the indirect treatment comparisons submitted by the sponsor included this comparison, the evidence from this indirect comparison is interpreted with caution.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review Should patients currently receiving first-line treatment for unresectable or metastatic melanoma with no disease progression be eligible to switch to nivolumab-relatlimab?	pERC agreed with the clinical experts that patients currently receiving first-line treatment for unresectable or metastatic melanoma with no disease progression would not be eligible to switch to nivolumab-relatlimab.
Should patients who experience toxicity with ipilimumab and discontinue ipilimumab without progression be able to switch to nivolumab-relatlimab?	pERC agreed with the clinical experts that patients who experience toxicity with ipilimumab and discontinue ipilimumab without progression would continue with nivolumab alone and would not be able to switch to nivolumab-relatlimab.
Should patients being treated with second-line pembrolizumab or nivolumab (when BRAF-targeted therapy was used in the first line) be eligible to switch to nivolumab-relatlimab?	pERC noted that this question is out of scope because the Health Canada indication is specific to first-line therapy as well as the evidence reviewed.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs.	Comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in previous lines.	Comment from the drug programs to inform pERC deliberations.
Drug may change place in therapy of drugs reimbursed in subsequent lines. Will patients be eligible for single-drug ipilimumab after progression? Will patients be eligible for any other ICI therapy after progression? Will patients with *BRAF* mutation be eligible for BRAF-targeted therapy after progression?	pERC noted that these questions are out of scope for the current CADTH review, which is focused on nivolumab-relatlimab in 1 particular line of therapy. However, pERC recognized the value of ipilimumab monotherapy in the second-line setting. pERC noted that provinces could address this with an updated funding algorithm.
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	Comment from the drug programs to inform pERC deliberations.
Other aspects.	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Companion diagnostics (e.g., access issues, timing of testing) Will LAG-3 testing be necessary?	pERC agreed with the clinical experts that LAG-3 testing is not necessary.
Other care provision issues In the event of toxicity to nivolumab-relatlimab, would switching to single-drug nivolumab be reasonable and/or permitted?	pERC agreed with the clinical experts that if toxicity is deemed to be related to relatlimab by the clinician, then it would be reasonable for the patient to switch to single-drug nivolumab.
System and economic issues	
Additional costs to be considered (other than related to care provision as detailed previously) Possible need for and cost of implementing LAG-3 testing in practice.	Comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	pERC response
Presence of confidential negotiated prices for comparators Confidential prices for other first-line therapies (ICI and BRAF-targeted therapies).	Comment from the drug programs to inform pERC deliberations.

BRAF = B-Raf proto-oncogene; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; IFN = interferon; IHC = immunohistochemistry; LAG-3 = lymphocyte-activation gene 3; NGS = next-generation sequencing; PD-L1 = programmed death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review pCODR Expert Review Committee; RECIST 1.1 = Response Evaluation Criteria in Solid Tumours Version 1.1.

Clinical Evidence

Systematic Review

Description of Studies

One pivotal, phase II/III, double-blinded, randomized controlled and ongoing trial (the RELATIVITY-047, N = 714) is included in the systematic review. The objective of RELATIVITY-047 was to evaluate the comparative efficacy and safety of nivolumab-relatlimab FDC) versus nivolumab monotherapy administered as a first-line therapy in the treatment of adult and pediatric patients 12 years of age or older with previously untreated, unresectable, or metastatic melanoma. However, no adolescents (aged ≥ 12 to < 18 years) were enrolled. A total of 714 patients were randomized 1:1 to receive nivolumab-relatlimab FDC (n = 355) or nivolumab monotherapy (n = 359). The median age was 63 years (range, 20 to 94 years). The majority (n = 655; 91.7%) of patients had metastatic stage IV cancer at study entry. The medium duration from diagnosis to the study treatment was 1.26 years. A total of 62 (8.7%) patients received previous adjuvant or neoadjuvant treatment. A total of 275 (38.5%) patients were *BRAF* positive. A total of 16 (2.2%) patients from Canada and 63 (8.8%) patients from the US were included. The primary outcome was PFS. The 2 secondary outcomes were OS and ORR. Tertiary or exploratory outcomes included duration of response (DOR), time to response (TTR), and HRQoL measurements (i.e., FACT-M, EQ-5D-3L). The sample size for the study was based on a primary end point of PFS using blinded independent central review for both phase II and phase III studies. Results presented in this submission reflect the phase III component of RELATIVITY-047. The final analysis for PFS was conducted after a median follow-up of 13.2 months. The final analysis for OS and ORR was conducted after a median follow-up of 19.3 months. Results for median DOR and TTR are based on the updated descriptive analysis conducted after a median follow-up of 25.3 months. HRQoL measurements (i.e., FACT-M, EQ-5D-3L) were conducted after a median follow-up of 19.3 months. The objective of the safety outcomes was to assess the overall safety and tolerability of nivolumab-relatlimab and nivolumab. Safety data reported in this review were based after a median follow-up of 25.3 months.

Efficacy Results

Based on the final analysis after a median follow-up of 13.2 months, the median PFS was 10.12 months (95% CI, 6.37 to 15.74 months) in the nivolumab-relatlimab FDC group, which was statistically significantly and clinically meaningfully longer compared to 4.63 months in the nivolumab monotherapy group (nivolumab-relatlimab FDC versus nivolumab: HR = 0.75; 95% CI, 0.62 to 0.92; P = 0.0055). The observed PFS benefit of nivolumab-relatlimab FDC compared with nivolumab monotherapy was shown in an updated descriptive

analysis after a median follow-up of 25.3 months. Subgroup and sensitivity analyses of PFS were largely consistent with the primary analysis.

After a median follow-up of 19.3 months, the median OS was not reached in the nivolumab-relatlimab group compared to 34.10 months in the nivolumab group. The between-group difference (nivolumab-relatlimab FDC versus nivolumab) for median OS did not reach statistical significance at the OS final analysis after a median follow-up of 19.3 months (HR = 0.80; 95% CI, 0.64 to 1.01; P = 0.0593). Similarly, after a median follow-up of 25.3 months, median OS was not reached in the nivolumab-relatlimab group compared to 33.18 months in the nivolumab group in updated descriptive analysis. Therefore, the comparative OS of nivolumab-relatlimab FDC compared with nivolumab monotherapy was uncertain.

Based on descriptive final analyses, a total of 10.3% (95% CI, 3.4% to 17.3%) more patients in the nivolumab-relatlimab FDC group achieved an objective response compared with those in the nivolumab group after a median follow-up of 19.3 months. Consistent ORR benefit was also observed in the updated descriptive analysis after a median follow-up of 25.3 months. A total of 9.8% (95% CI, 2.8% to 16.8%) more patients in the nivolumab-relatlimab FDC group achieved an objective response compared with the nivolumab group.

In terms of complete response and progressive disease, no formal statistically analysis or any descriptive analysis was done to report the between-group difference or 95% CI of between-group difference. No HR (95% CI) was provided. Therefore, the comparative complete response and progressive disease of nivolumab-relatlimab FDC compared with nivolumab monotherapy remains inconclusive.

After a median follow-up of 25.3 months, no statistical and clinical meaningful between-group difference was observed for DOR. TTR appeared the same after a median follow-up of 25.3 months. However, no between-group difference and no HR was reported for TTR. The comparative DOC and TTR of nivolumab-relatlimab FDC compared with nivolumab monotherapy remain uncertain.

After a median follow-up of 19.3 months, HRQoL (FACT-M, EQ-5D-3L utility index scores and EQ-5D-VAS) in the nivolumab-relatlimab FDC and nivolumab groups remained generally stable (no clinical meaningful improvement or deterioration) during the treatment period. There were little to no differences between nivolumab-relatlimab FDC and nivolumab monotherapy in FACT-M, EQ-5D-3L utility index scores, and EQ-5D-VAS.

No adolescents (aged ≥ 12 to 18 years) were enrolled in the pivotal study. However, in the Health Canada product monograph, the indication of nivolumab-relatlimab FDC includes for the use for pediatric patients 12 years of age or older and weighing at least 40 kg. In the product monograph, it was indicated that use of nivolumab-relatlimab FDC in pediatric patients is supported by predicted drug exposures at the recommended nivolumab-relatlimab FDC dose that are expected to result in similar safety and efficacy to that of adults. The safety and efficacy of nivolumab-relatlimab FDC have not been established in pediatric patients younger than 12 years or in patients 12 years or older and weighing less than 40 kg.

Harms

The proportion of patients with at least 1 treatment-emergent AE appeared similar in the nivolumab-relatlimab FDC group compared with the nivolumab monotherapy group (99.2% in the nivolumab-relatlimab

FDC group versus 95.8% in the nivolumab monotherapy group). However, the most common any-grade AEs (occurred in > 20% patients in either of the 2 groups) appeared to occur in more patients in the nivolumab-relatlimab FDC group than the nivolumab monotherapy group, such as fatigue (nivolumab-relatlimab FDC versus nivolumab: 30.7% versus 20.9%) and diarrhea (27.9% versus 19.5%). The frequency of serious AEs (SAEs) appeared similar in both groups, and individual SAE events were relatively rare. With the exception of malignant neoplasm progression (nivolumab-relatlimab FDC versus nivolumab: 3.9% versus 5.6%), there were no other SAEs that occurred in more than 2% of patients in either group. The frequency of withdrawal due to AEs also appeared numerically higher in the nivolumab-relatlimab FDC group than in the nivolumab monotherapy group (nivolumab-relatlimab FDC versus nivolumab: 23.1% versus 15.9%). Discontinuation treatment due to specific AEs occurred in less than 2% patients in either of the groups, with the exception of malignant neoplasm progression (nivolumab-relatlimab FDC versus nivolumab: 1.7% versus 2.8%). The frequency of death due to AEs (i.e., study drug toxicity) was rare in both groups (nivolumab-relatlimab FDC versus nivolumab: 1.1% versus 0.6%). Adrenal insufficiency was considered as particular special immune-mediated adverse event, which occurred numerically higher in the nivolumab-relatlimab FDC group than in the nivolumab group (5.6% versus 1.1%). The other particular notable harm, myocarditis, rarely occurred (1.7% versus 0.6%). Grade 3 or 4 all-causality AEs were numerically more frequent with nivolumab-relatlimab FDC versus nivolumab (nivolumab-relatlimab FDC versus nivolumab: 44.8% versus 36.8%). Overall, the safety profile of nivolumab-relatlimab FDC was considered manageable and consistent with the known mechanisms of action of relatlimab or nivolumab. No new safety signal was identified.

Critical Appraisal

Appropriate methods of randomization, blinding, and allocation concealment were reported. Objective outcomes and validated health-related outcomes were assessed. However, a minimal important between-group difference, which is the threshold used for the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for all outcomes, are not available. Therefore, clinical expert opinion informed the thresholds to determine whether the between-group difference observed for each outcome was clinically meaningful or not.

Metastatic stage M1c was relatively higher in the nivolumab-relatlimab FDC group (n = 151; 42.5%) than in the nivolumab monotherapy group (n = 127; 35.4%); however, the clinical experts consulted for this review stated that minor between-group imbalances of metastatic stage M1c would have been unlikely to impact the comparative study results between the nivolumab-relatlimab FDC and nivolumab monotherapy groups.

In terms of the OS assessment, OS was designed and assessed as a secondary outcome, the study was not powered to assess OS between-group differences at the prespecified final analysis (after a median follow-up of 19. 3 months) and updated analysis (after a follow-up of 25.3 months). Therefore, the comparative efficacy on OS of nivolumab-relatlimab FDC compared with nivolumab remains uncertain.

The statistical significance of ORR (per blinded independent central review) could not be formally tested due to its position in the statistical hierarchy because the OS final analysis did not reach statistical significance. As a result, ORR, as well as complete response and progressive disease (which were part of the overall response analysis), are based on only descriptive analyses after a median follow-up of 19.3 months. Only

descriptive analyses without between-group differences or HRs were reported. Therefore, results on ORR, complete response, and progressive disease should be interpreted with caution.

DOR and TTR were assessed as tertiary or exploratory outcomes but were not controlled for the hierarchical testing procedure to control type I error. Analyses of DOR and TTR were not statistically powered, and they were reported using descriptive statistics only. No between-group differences were reported for DOR or TTR, although HR was reported for DOR. Overall, the findings of DOR and TTR should be viewed as supportive evidence only.

Similarly, FACT-M and EQ-5D-3L were assessed as tertiary or exploratory outcomes but were not controlled for the hierarchical testing procedure to control type I error. For those patients that reported HRQoL outcomes (FACT-M and EQ-5D-3L), there may have been differential recall bias. Overall, the magnitude and direction of the impact of the recall bias on the patient-reported HRQoL outcomes is unknown. HRQoL analyses were not statistically powered and were reported using descriptive statistics. Overall, the findings of HRQoL should be viewed as supportive evidence only.

All subgroup analyses were not part of the randomization scheme; therefore, imbalances in characteristics may bias the results observed between the subgroups. In addition, the subgroup analyses may not be powered to detect between-group differences in each subgroup. Therefore, the findings of the subgroup analyses should be viewed as supportive evidence only.

In addition, 1 of the limitations of the RELATIVITY-047 trial is lack of comparison to current standard-of-care therapy, except nivolumab monotherapy, the comparative efficacy and safety of nivolumab-relatlimab FDC compared with nivolumab-ipilimumab, encorafenib-binimetinib, dabrafenib-trametinib, vemurafenib-cobimetinib, ipilimumab, pembrolizumab, dabrafenib, and trametinib is unknown.

It is uncertain whether the finding can be generalized to patients with CNS metastases or patients with ECOG performance status greater than 1 because patients with these were not included in the study. Only 17 (2.4%) patients with brain metastasis were included (1.7% and 3.1% in the nivolumab-relatlimab FDC group and nivolumab monotherapy group, respectively). Patients with active CNS metastases were excluded. The clinical experts CADTH consulted for this review indicated that although higher ECOG performance status (> 1) usually indicates more severe disease and more likely with unfavourable prognosis, that the nivolumab-relatlimab FDC combination treatments could be extended to patients with ECOG greater than 1. In terms of patients with CNS metastasis, the clinical experts CADTH consulted for this review indicated that additional studies are needed to understand the comparative efficacy and safety of nivolumab-relatlimab FDC versus nivolumab monotherapy in patients with CNS metastasis.

Finally, although age 12 years or older was an inclusion criterion, no children (≥ 12 years to < 18 years) were enrolled in the pivotal study. Therefore, the comparative efficacy and safety profile of nivolumab-relatlimab FDC versus nivolumab monotherapy is unknown whether the findings from the RELATIVITY-047 trial can be generalized to adolescent patients (≥ 12 years to < 18 years) remains unknown. However, in the Health Canada product monograph, it is indicated that the use of nivolumab-relatlimab FDC in pediatric patients aged 12 years or older and weighing at least 40 kg is supported by predicted drug exposures at the

recommended nivolumab-relatlimab FDC dose that are expected to result in similar safety and efficacy to that of adults. One clinical expert CADTH consulted for this review indicated that pediatric patients with unresectable or metastatic melanoma should be enrolled in clinical trials, if available, to assess the efficacy and safety profile of the nivolumab-relatlimab FDC treatment. The other clinical expert CADTH consulted for this review indicated that because of the potential unfeasibility of the trials on the pediatric patients, use of nivolumab-relatlimab FDC in adolescents should be considered on a case-by-case basis — especially if body habitus is similar to an adult or close to that of an adult. The clinical expert noted that currently immuno-oncology (IO) agent is given in the pediatric population, and it is well tolerated.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform CADTH's expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group. Following the GRADE approach, evidence from randomized controlled trials started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

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: PFS, OS, ORR, DOR, and HRQoL (i.e., FACT-M, EQ-5D-3L utility index, and EQ-5D-VAS) change from cycle baseline after a median follow-up of 19.3 months and at a fixed landmark time point of 24 months as well as notable harms (i.e., myocarditis and adrenal insufficiency).

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. For this review, the target of the certainty of evidence assessment was based on the presence or absence of a clinically important effect, as informed by minimum important differences (MIDs) and thresholds suggested by the clinical experts (for all outcomes). Results of GRADE Assessments are presented in Table 3.

Table 3: Summary of Findings for Nivolumab–Relatlimab Versus Nivolumab Monotherapy in Adult and Pediatric Patients With Unresectable or Metastatic Melanoma Without Prior Systemic Therapy

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Nivolumab	Nivolumab-relatlimab	Difference		
PFS							
PFS per BICR using RECIST 1.1 Median follow-up: 13.2 months	714 (1 RCT)	PFS events (i.e., disease progression or death) at data cut-off: • Nivolumab-relatlimab: 507 per 1,000 • Nivolumab: 588 per 1,000 • HR = 0.75 (95% CI, 0.62 to 0.92) PFS at data cut-off (months): • Nivolumab-relatlimab: median = 10.12 (95% CI, 6.37 to 15.74) • Nivolumab: median = 4.63 (95% CI, 3.38 to 5.62)				High[a]	Nivolumab-relatlimab results in a clinically important increase in PFS when compared with nivolumab monotherapy.
OS							
OS per DMC Median follow-up: 19.3 months	714 (1 RCT)	OS events (i.e., deaths) at data cut-off: • Nivolumab-relatlimab: 386 per 1,000 • Nivolumab: 446 per 1,000 • HR = 0.80 (95% CI, 0.64 to 1.01) OS at data cut-off (months): • Nivolumab-relatlimab: median = NA (95% CI, 34.20 to NA) • Nivolumab: median = 34.10 (95% CI, 25.23 to NA)				Low[b]	Nivolumab-relatlimab may result in a clinically important increase in OS when compared with nivolumab monotherapy.
ORR							
ORR (CR + PR) per BICR using RECIST 1.1 Median follow-up: 19.3 months	714 (1 RCT)	OR = 1.58 (95% CI, 1.16 to 2.15)	326 per 1,000	431 per 1,000 (95% CI, 379 to 484 per 1,000)	103 more per 1,000 (95% CI, 34 to 173 more per 1,000)	Moderate[c]	Nivolumab-relatlimab likely results in a clinically important increase in ORR when compared with nivolumab monotherapy.

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Nivolumab	Nivolumab-relatlimab	Difference		
DOR							
DOR per BICR using RECIST 1.1 Median follow-up: 25.3 months	276 (1 RCT)	DOR events (i.e., progression or death following first response) at data cut-off: • Nivolumab-relatlimab: 335 per 1,000 • Nivolumab: 314 per 1,000 • HR = 1.07 (95% CI, 0.71 to 1.63) DOR at data cut-off (months) • Nivolumab-relatlimab: median = NA (95% CI, 39.36 to NA) • Nivolumab: median = NA (95% CI, 39.82 to NA)				Low[d]	Nivolumab-relatlimab may result in little to no difference in DOR when compared with nivolumab monotherapy.
HRQoL (median follow-up = 19.3 months; fixed landmark time points = 24 months)							
FACT-M							
FACT-M total score Mean change from baseline (0 = worst HRQoL; 204 = best HRQoL) Median follow-up: 19.3 months	151 (1 RCT)	NR	3.563	1.756 (95% CI, −1.763 to 5.275)	−1.807 (95% CI, −6.561 to 2.947)	Low[e]	Nivolumab-relatlimab may result in little to no difference in HRQoL as measured by the FACT-M when compared with nivolumab monotherapy.
EQ-5D-3L utility index							
EQ-5D-3L utility score Mean change from baseline (0 = as bad as dead; 1 = perfect health) Median follow-up: 19.3 months	150 (1 RCT)	NR	0.002	0.009 (95% CI, −0.036 to 0.053)	0.007 (95% CI, −0.052 to 0.066)	Low[e]	Nivolumab-relatlimab may result in little to no difference in HRQoL as measured by EQ-5D-3L utility values when compared with nivolumab monotherapy.
EQ-5D-3L VAS							
EQ-5D-3L VAS Mean change from	150 (1 RCT)	NR	2.084	2.840 (95% CI, −0.454 to 6.135)	0.757 (95% CI, −3.651 to 5.164)	Low[e]	Nivolumab-relatlimab may result in little to no

Outcome and follow-up	Patients (studies), N	Relative effect	Absolute effects			Certainty	What happens
			Nivolumab	Nivolumab-relatlimab	Difference		
baseline (0 = worst health imaginable; 100 = best health imaginable) Median follow-up: 19.3 months							difference in HRQoL as measured by the EQ-5D-3L VAS when compared with nivolumab monotherapy.
Notable harms (i.e., AEs of special interest)							
Myocarditis Median follow-up: 25.3 months	714 (1 RCT)	NR	6 per 1,000	17 per 1,000 (NR)	NR	Low[f]	Nivolumab-relatlimab may result in an increase in the proportion of patients who experience myocarditis when compared with nivolumab monotherapy. The clinical importance of the increase is uncertain.
Adrenal insufficiency Median follow-up: 25.3 months	714 (1 RCT)	NR	11 per 1,000	56 per 1,000 (NR)	NR	Low[f]	Nivolumab-relatlimab may result in an increase in the proportion of patients who experience adrenal insufficiency when compared with nivolumab monotherapy. The clinical importance of the increase is uncertain.

AE = adverse event; CI = confidence interval; DOR = duration of response; FACT-M = Functional Assessment of Cancer Therapy – Melanoma; HRQoL = health-related quality of life; NA = not available (or not reached); NR = not reported; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumours; VAS = visual analogue scale.

Note: The analysis of ORR, DOR, and HRQoL (FACT-M total score and EQ-5D-3L) were not adjusted for multiple comparisons.

[a]In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the hazard ratio (HR) using the null as the threshold. The clinical importance of the between-group difference was judged based on the input of the clinical experts consulted by CADTH for the review.

[b]Rated down 1 level for serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The 95% CI for the HR included the possibility of little to no difference (i.e., included the null). The clinical importance of the between-group difference was judged based on the input of the clinical experts consulted by CADTH for the review. Rated down 1 level for serious indirectness. The follow-up time was not sufficient for assessing OS in this population.

[c]Rated down 1 level for serious imprecision. Based on the threshold for a clinically important between-group difference suggested by the clinical experts of 50 events per 1,000 patients to 100 events per 1,000 patients, the point estimate suggests a benefit; however, the lower bound of the 95% CI suggests little to no difference.

[d]Rated down 2 levels for very serious imprecision. In the absence of available data for the between-group difference in event probabilities at clinically relevant time points, the judgment of imprecision was based on the 95% CI for the HR using the null as the threshold. The 95% CI for the HR included the possibility of both benefit and harm for nivolumab-relatlimab compared with nivolumab monotherapy.

[e]Rated down 2 levels for very serious risk of bias due to missing outcome data. Data were available for 21% of randomized patients. In the absence of a known threshold for a clinically important between-group difference, the null was used as the threshold.

[f]Rated down 2 levels for very serious imprecision. The results are based on very few events in each group (6 of 355 vs. 2 of 359 for myocarditis and 20 of 355 vs. 4 of 359 for adrenal insufficiency in the nivolumab-relatlimab and nivolumab groups, respectively).

Long-Term Extension Studies

This information is not available.

Indirect Comparisons

Description of Studies

Overall, 2 ITC reports were submitted. One ITC, a Bayesian network meta-analysis, assessed the safety and efficacy of nivolumab-relatlimab relative to other IO agents for adult patients in the first-line management of patients with advanced melanoma. The second ITC, a patient-level propensity-weighted comparison, assessed nivolumab-relatlimab relative to nivolumab-ipilimumab among patients with advanced melanoma treated in first line.

Efficacy Results

The first ITC, a Bayesian network meta-analysis assessed nivolumab-relatlimab relative to nivolumab monotherapy, ipilimumab monotherapy, nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg), nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg), pembrolizumab-cobimetinib plus atezolizumab.

The first ITC indicated that nivolumab-relatlimab is associated with improvements to OS relative to ipilimumab monotherapy at 48 months (HR = 0.48; 95% credible interval [CrI], 0.34, 0.69). For PFS at 48 months, nivolumab-relatlimab is associated with improvements relative to ipilimumab (HR = 0.32; 95% CrI, 0.22 to 0.48), pembrolizumab (HR = 0.59; 95% CrI, 0.35 to 0.97), and [redacted].

For the second ITC, the results indicated that there was no difference between nivolumab-relatlimab relative to ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) with respect to PFS and OS.

No data were available in either ITC with respect to ORR, time to progression, or any patient-reported outcome.

Harms Results

In the first ITC, nivolumab-relatlimab was associated with higher proportions of patients having grade 3 to 4 treatment-related AEs when compared to nivolumab (OR = 2.08; 95% CrI, 1.39 to 3.14), [redacted] and pembrolizumab (OR = 1.99; 95% CrI, 1.01 to 3.87), and was associated with lower proportions of patients experiencing these events relative to nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) (OR = 0.43; 95% CrI, 0.25 to 0.73). For discontinuations due to AEs, [redacted].

No comparative data were presented from the second ITC with respect to safety outcomes, as no formal statistical comparison of the differences in safety events were conducted.

Critical Appraisal

Sponsor-submitted evidence from the first ITC was provided with comparisons to non-IO interventions of interest, such as BRAF and MEK inhibitors, but owing to several challenges associated with mixed mutation status and the evidence from treatment nodes connecting to this network of evidence, no clear conclusions could be drawn with respect to comparative efficacy and safety within this population. Several trials reporting on OS for the IO network of evidence still had ongoing observation for survival data at the time of analysis, so there may be additional uncertainty with these comparisons.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult and pediatric patients (12 years and older and weighing at least 40 kg) with unresectable or metastatic melanoma
Treatment	Nivolumab-relatlimab
Dose regimen	480 mg nivolumab and 160 mg relatlimab every 4 weeks until disease progression or unacceptable toxicity
Submitted price	Nivolumab 240 mg plus relatlimab 80 mg, in a fixed-dose combination: $8,315 per 20 mL vial
Treatment cost	$16,630 every 28 days
Comparators	Nivolumab monotherapy Ipilimumab monotherapy Pembrolizumab monotherapy Nivolumab-ipilimumab Vemurafenib-cobimetinib Dabrafenib-trametinib Encorafenib-binimetinib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (25 years)
Key data sources	RELATIVITY-047 Sponsor-submitted systematic review and NMA
Key limitations	The CADTH clinical review could not reach definitive conclusions regarding relative treatment efficacy for nivolumab-relatlimab compared with relevant comparators for OS or PFS outcomes. Additionally, a stratified analysis should have been conducted given that some comparator treatments are indicated for the *BRAF*-positive subpopulation. Issues with the sponsor's modelling approach: • Predicted values for the OS curve were capped by the general population mortality risk, which was

Component	Description
	inappropriate for a partitioned survival model and impedes the model's ability to properly reflect transitions between health states. • The sponsor used a 2-part extrapolation approach for PFS in their model, which is not recommended by CADTH submission guidelines. The use of such an approach hinders the ability of the model to reflect decision uncertainty. • Use of the Gompertz distribution to predict long-term survival implied that some patients would be cured as a result of treatment. Clinical experts consulted by CADTH suggested less optimistic predictions of long-term survival were required.
CADTH reanalysis results	The CADTH base case addressed some of the key identified limitations: the cap on predicted OS values was removed; predicted PFS values for and nivolumab were generated from a parametric survival model; and predicted values for OS and PFS for nivolumab-relatlimab and nivolumab monotherapy were assumed to follow an exponential, rather than a Gompertz distribution. In the CADTH base case, 3 treatments were identified to be on the cost-effectiveness frontier. Nivolumab-relatlimab was the most costly and the most effective. A price reduction for nivolumab/relatlimab is required to be considered cost-effective at a willingness to pay threshold of $50,000 per QALY gained.

FDC = fixed-dose combination; LY = life-year; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: uncertainty in estimates of market size resulting from assuming 92.67% of patients will be diagnosed at stage I to III (resectable), [redacted] of patients will recur to stage III (unresectable) or stage IV following an initial diagnosis of stage I to III (resectable), and [redacted] of patients will be diagnosed at stage III (unresectable).

CADTH performed a reanalysis, which explored how changes in each assumption affected the estimated budget impact. Clinical experts consulted by CADTH assumed 85% of patients will be diagnosed at stage I to III (resectable), 5% of patients will recur to stage III (unresectable) or stage (IV) following an initial diagnosis of stage I to III (resectable), and 10% of patients will be diagnosed at stage III (unresectable).

Based on the CADTH base case, the budget impact from the introduction of nivolumab-relatlimab is expected to be $4,734,946 in year 1, $12,890,614 in year 2, and $16,679,027 in year 3. The 3-year net budget impact was estimated to be $34,304,588.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip 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.

Meeting date: December 5, 2023

Regrets: 3 expert committee members did not attend.

Conflicts of interest: None

ISSN: 2563-6596

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